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Physiological Studies in Congenital Heart Disease. X. The Physiological Findings in Thirty-four Patients with Isolated Pulmonary Valvular Stenosis. F. Maraist, R. Daley, A. Draper, Jr., R. Heimbecker, F. Dammann, Jr., R. Kieffer, Jr., J. Talbot King, C. Ferencz, and R. J. Bing 1

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PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE

X. The Physiological Findings in Thirty-four Patients with Isolated Pulmonary Valvular Stenosis*

F. MARAIST,[1] R. DALEY,[2] A. DRAPER Jr.,[3] R. HEIMBECKER,[4] F. DAMMANN Jr.,[5] R. KIEFFER Jr., J. TALBOT KING,[6] C. FERENCZ[7] and R. J. BING

Department of Surgery, the Johns Hopkins University School of Medicine and Hospital

Received for publication September 1, 1950

With the development of the technique of valvulotomy for the relief of congenital pulmonary valvular stenosis (1) an accurate differential diagnosis between isolated pulmonic stenosis and the Tetralogy of Fallot has become of great importance.

Anatomically, the Tetralogy of Fallot is characterized by a ventricular septal defect and an overriding aorta. The pulmonic stenosis is usually infundibular. Physiologically, there is a decrease in the pulmonary arterial and the effective pulmonary blood flow. The overall direction of the intracardiac shunt is from right to left although there is commonly a small left to right shunt. The reduction in the ratio of effective flow to systemic flow results in a decrease of the peripheral arterial oxygen saturation (2). The construction of an artificial ductus (3) gives a channel through which unoxygenated blood can pass from the aorta to the lungs. Hence, following operation, there is an increase in the effective pulmonary flow and as the ratio of effective pulmonary to systemic flow increases, so also does the peripheral arterial oxygen saturation.

* This work has been supported by grants issued by the Commonwealth Fund, the Carolyn Rose Strauss Foundation, and the Gulftex Foundation and the U. S. Public Health Service to the Department of Surgery of the Johns Hopkins Hospital and University.

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[7] Fellow of the U. S. Public Health Service.

In isolated pulmonic valvular stenosis the foramen ovale may be open or closed. In both types of malformations, the stenosis is usually at the pulmonic valve. The valve is replaced by a dome-like diaphragm across the orifice, which projects into the pulmonary artery. In the center of the diaphragm there is usually a small slit seldom larger than a few millimeters in diameter.

The clinical and pathological findings in a series of cases of pulmonic stenosis with and without patent foramen ovale have been reported by Selzer and associates (4). Greene and associates presented a series of cases of pulmonic stenosis without abnormal shunts in 1949. (5). The purpose of this work is to report the results of the physiological studies performed on thirty-four patients with pulmonic valvular stenosis in this laboratory during the past four years. The findings will be discussed with reference to their diagnostic value. Special emphasis will be placed on the difference in dynamics between patients in whom the foramen ovale is closed and those in whom it is patent.

The patients in this study are divided into two groups:

1. Those in whom the diagnosis has been proven either at postmortem examination or at operation.

2. Those in whom the diagnosis was not confirmed by operative or postmortem examination. In this group the diagnosis was made on the basis of complete clinical and physiological studies. Each of these groups is subdivided on the basis of physiological findings into those who have patency of the foramen ovale, and those in whom the foramen ovale is closed.

METHODS

The methods employed in these studies have been described in detail in the first paper of the series (6). The terms and foramulae used in determing blood flows by the Fick principle are redefined for the sake of clarity:

$$\text{Systemic flow (ml./min.)} = \frac{\text{Oxygen uptake (ml./min.)} \times 100}{\text{Oxygen content of peripheral arterial blood (vol.\%)} - \text{Oxygen content of mixed venous blood (vol.\%)}}$$

The pulmonary artery blood flow is the volume of blood passing through the pulmonary artery per minute:

$$\text{PA flow (ml./min.)} = \frac{\text{Oxygen uptake (ml./min.)} \times 100}{\text{Oxygen content of pul. vein blood (vol.\%)} - \text{Oxygen content of pul. artery blood (vol.\%)}}$$

The effective pulmonary blood flow is the volume of mixed venous blood which, after returning to the right auricle, eventually reaches the pulmonary capillaries.

$$\text{Eff. pul. flow (ml./min.)} = \frac{\text{Oxygen uptake (ml./min.)} \times 100}{\text{Oxygen content of pul. vein blood (vol.\%)} - \text{Oxygen content of mixed venous blood (vol.\%)}}$$

The total right to left shunt is the volume of mixed venous blood which is shunted into the systemic circulation per minute.

$$\text{Total R-L shunt} = \text{systemic flow} - \text{effective pulmonary flow}$$

The total left to right shunt is the volume of fully oxygenated blood which is shunted into the pulmonary circulation per minute.

$$\text{Total L-R shunt} = \text{Pulmonary flow} - \text{effective pulmonary flow}$$

The overall shunt is the difference in the volume of the pulmonary artery and systemic blood flow which has resulted from shunting. In all cases of isolated pulmonic stenosis the overall shunt if present is right to left, and in most cases it is equal to the total right to left shunt.

Certain assumptions have to be made in calculating flows from these formulae. Usually it is impossible to obtain a blood sample from a pulmonary vein but in the absence of significant pulmonary disease the saturation of the pulmonary venous blood is assumed to be 96 per cent. This assumption is based on the values obtained for the oxygen saturation of pulmonary venous blood in twenty-four patients in whom pulmonary veins were directly catheterized in this laboratory (7). When the pulmonary artery could not be catheterized, the oxygen content of the sample taken from the right ventricular outflow tract was used in calculating the pulmonary blood flow.

Blood samples were obtained by cardiac catheterization and arterial puncture. Blood oxygen contents were determined by the method of Van Slyke and Neill (8). Expired air was collected in Douglas Bags. The carbon dioxide content was determined in the Haldane apparatus (9), and the oxygen content was determined with the Pauling Oxygen analyzer. All volumes were expressed in terms of dry gas at 760 mm. Hg. and 0° Centigrade. Intracardiac pressures were measured by means of strain gauges and recorded optically by oscillograph galvanometers.

Since it is impossible to determine the mean systolic pressure in the right ventricle, the resistance of the pulmonic valve cannot be calculated. For comparative purposes, therefore, the right ventricular work per square meter of body surface may be expressed in arbitrary units.

$$\text{R.V. work (arbitrary units)} = \text{R.V. systolic pressure} \times \text{pul. flow in } L/M^2/\text{min.}$$

By inserting into this formula normal values, an arbitrary figure of 75 is calculated for the work of the normal right ventricle.

$$\text{R.V. work}/M^2 \text{ (arbitrary units)} = 25 \times 3.0 = 75$$

The findings obtained by cardiac catheterization of thirty-four patients with pulmonic valvular stenosis are summarized in Table I to V, and in Figure 1. The

TABLE I

Data Obtained From Cardiac Catherization of Eight Patients with Pulmonary Valvular Stenosis with Closed Foramen Ovale

	PATIENT	SEX	AGE	SURFACE AREA M^2	O_2 CONS. CC./MIN.	OXYGEN CONTENT IN VOLUMES PER CENT											BLOOD FLOW IN CC./MIN./M^2			SHUNTS CC./MIN./M^2		PRESSURE MM./HG		R.V. WORK
						S.V.C.	I.V.C.	R.A.	R.V. in	R.V. out	P.A.	L.A.	P.V.	O_2 cap.	F.A.	% Sat.	Syst.	Pul.	Eff.	R-L	L-R	R.V.	P.A.	
Proven oper.	1) C. B.	M	13	1.44	247	9.31		9.33	8.54	8.44	9.16		9.16	19.88	19.00	95.6	1710	1710	1710	0	0	143/0	21/9	244
Proven oper.	2) J. D.	F	20	1.53	137	8.65	11.79	9.95	10.68	8.00	13.40		21.70*	22.80	21.70	95.5	775	775	775	0	0	198/20	mean 8	154
Proven Autopsy	3) C. C.	M	30	1.80	288	9.40	7.80	8.00	8.80				18.80*	19.80	18.60	94.0	1750	1750	1750	0	0			
	Average	M–F														95.0	1412	1412	1412	0	0	171/10	mean 11	242
Unproven Cases	4) M. L.	F	8	0.85	150	11.71	14.80	12.51	11.11	10.50	11.08	16.07	16.39	17.15	16.30	95.0	3400	3400	3400	0	0	134/11	22/7	455
	5) R. A.	F	6	0.90	141	10.79	12.12	10.08	10.81		10.45		15.22*	15.91	15.12	95.9	2070	2070	2070	0	0	74/0	24/12	153
	6) D. N.	F	6	0.83	157	11.23	12.93	11.27	11.86	11.74	10.24	14.84	14.68*	14.84	14.68	99.0	5180	5180	5180	0	0	82/6	20/12	425
	7) R. S.	M	7	0.91	104	11.99		13.77	13.11	12.52	13.22		16.80*	17.50	16.64	95.0	3380	3380	3380	0	0	72/20	24/9	243
	8) H. C.	M	6	0.90*	120*	13.70	14.20	14.20		12.90	12.20		17.20*	17.60	17.20	97.6	3100	3100	3100	0	0	56/5	25/15	174
	Average	M–F														96.5	3426	3426	3426	0	0	84/10	23/11	290
	Normal															96.0	3000	3000	3000	0	0	25/0	25/8	75

(* Indicates assumed figures for Oxygen consumption in cc./minute or for oxygen content in the pulmonary veins.)

TABLE II

Data obtained from cardiac catheterization of twelve patients with pulmonary valvular stenosis with patent foramen ovale proven at operation

PATIENT	SEX	AGE	SURF. AREA M^2	O_2 CONS. CC./MIN.	OXYGEN CONTENT IN VOLUMES PER CENT										BLOOD FLOW IN CC./MIN./M^2			SHUNTS IN CC./MIN./M^2		PRESSURES IN MM. HG.		R. V. WORK
					S.V.C.	I.V.C.	R.A.	R.V. in	R.V. out	P.A.	L.A.	P.V.	O_2 cap.	F.A.	% Sat.	Syst.	Pul.	Eff.	R-L	L-R	R.V.	P.A.	
1) M. K.	F	13	1.35	182	13.31	14.61	14.31	13.44	13.10	13.21		20.76*	21.61	20.22	93.5	1910	1770	1770	140	0	223/13	14/6	394
2) C. S.	F	6	0.70	100*	11.30		10.90	—				27.80*	28.61	19.30	67.5	1810	800	800	1010	0	162/45		163
3) R. A.	M	17	1.48	138	13.60		13.90	14.00				26.60*	28.00	24.00	86.0	920	740	740	180	0	143/18		106
4) C. S.	M	12	1.42	147	12.67		12.97	12.37				16.70*	17.20	16.08	93.5	2790	2390	2390	400	0	122/30		291
5) S. L.	F	1½	0.43	60*	8.06	6.58	7.48					18.50*	19.29	13.70	71.0	2220	1270	1270	950	0	84/60		107
6) K. F.	F	4	0.60	94	12.05	11.24	10.08	9.79	10.18			16.60*	17.29	15.92	92.3	2760	1460	1460	340	0	165/36		241
7) E. S.	F	7	0.87	114	11.83	11.79	11.60	10.22	11.77	8.14	18.97	19.10*	19.90	16.62	83.6	2700	1788	1788	912	0	166/26	mean 16	296
8) E. K.	F	6½	0.69	104.5	12.14	10.37	10.73	10.19	10.15			20.62*	21.49	14.14 crying	65.8	3800	1446	1446	2354	0	146/46		211
9) R. F.	F	5½	0.77	120*	12.01	15.88	16.30	17.85			27.8	28.88	28.88	17.90	62.0	4220	1415	1020	3200	395	90/0		127
10) A. V.	M	5½	0.76	108	15.90		16.51		16.18	16.30		29.00*	30.20	21.10	70.0	2960	1120	1120	1840	0	125/0	14/8	140
11) J. H.	M	4	0.73	100*	11.75		11.60	11.35	11.56	10.07		18.50*	19.30	17.02	88.5	2510	1975	1975	535	0	154/14	mean 13	304
12) S. S.	F	7½	0.86	126.4	12.20		13.12	12.44	12.89	10.91		21.00*	21.90	17.41	79.7	3260	1814	1814	1446	0	146/10	16/11	265
Aver.	4M–8F														79.5	2660	1517	1465	1194	51	144/25	15/8	220
Normal															96.0	3000	3000	3000	0	0	25/0	25/9	75

(* assumed figures for oxygen consumption in cc./min. or for pulmonary vein oxygen content.)

TABLE III

Data obtained from cardiac catheterization of seven patients with pulmonary valvular stenosis with patent foramen ovale later proven at autopsy

PATIENT	SEX	AGE	SURF. AREA M^2	O_2 CONS. CC./ MIN.	OXYGEN CONTENT IN VOLUMES PERCENT											BLOOD FLOW IN CC./MIN./M^2			SHUNTS IN CC./ MIN./M^2		PRESSURES IN MM. HG.		R. V. WORK
					S.V.C.	I.V.C.	R.A.	R.V. in	R.V. out	P.A.	L.A.	P.V.	O_2 cap.	F.A.	% Sat.	Syst.	Pul.	Eff.	R-L	L-R	R.V.	P.A.	
1) J. M.	M	8 mo.	0.35	50*	5.31		5.51	5.05	5.09		16.31	18.75*	19.57	16.31	83.2	1320	1070	1070	250	0	112/46		120
2) W. W.	M	23	1.88	204	18.60		15.00	14.30				28.60*	30.10	18.40	61.1	2640	760	760	1880	0			
3) D. L.	M	5	0.79	100*	9.20		10.30	12.20				22.20*	23.10	19.20	83.1	1830	1280	980	850	300	112/55		143
4) C. G.[1]	M	9	0.94	154	14.50		13.70	13.10				20.70*	22.00	18.50	84.1	3290	2280	2280	1010	0	72/30		164
[2]			1.20	162	13.42	12.89	11.64	12.15	12.20	11.98		27.90*	28.88	17.48	60.5	2440	850	850	1590	0	105/0	17/13	89
5) J. T.	F	9	0.82	120	12.54	13.34	11.36	12.07				24.95*	26.00	19.69	75.8	1930	1140	1140	790	0	191/30		218
6) G. K.	F	4	0.30	50*	12.35		13.27	13.00				19.95*	20.57	17.00	83.0	4470	2400	2400	2070	0	110/27		264
7) M. B.	F	18	1.31	122			12.50		12.50	15.40		24.90*	31.00	16.40	53.0	2400	665	550	1850	115	132/64		88
Aver.	3F–4M														73.0	2539	1306	1254	1273	52	119/36	17/13	155
Normal															96.0	3000	3000	3000	0	0	25/0	25/8	715

(* indicates assumed figures for oxygen consumption in cc./min. or for oxygen content in the pulmonary veins.)

TABLE IV

Data obtained from cardiac catheterization of seven patients with pulmonary valvular stenosis with patent foramen ovale; unproven

PATIENT	SEX	AGE	SURF. AREA M^2	O_2 CONS. CC./MIN.	OXYGEN CONTENT IN VOLUMES PER CENT											BLOOD FLOW IN CC./MIN./M^2			SHUNTS IN CC./MIN./M^2		PRESSURES IN MM. HG.		R.V. WORK
					S.V.C.	I.V.C.	R.A.	R.V. in	R.V. out	P.A.	L.A.	P.V.	O_2 cap.	F.A.	% SAT.	Syst.	Pul.	Eff.	R-L	L-R	R.V.	P.A.	
1) A. J.	M	7	0.67	132	8.90	8.62	9.14		12.79	8.80	14.45	14.80*	16.02[1]	14.56[1]	91.0[1]	3420	2460	2460	960	0	160/16	25/16	394
2) E. A.	M	11	1.08	139	9.21	9.16	10.38		10.41	10.68		15.60*	16.21	15.18	93.5	2860	2620	2620	240	0	193/0	30/18	506
3) J. D.	M	7	0.90	134	12.73		13.90	13.60	13.31	13.43		17.08*	17.79	16.36	92.0	5080	4080	4080	1000	0	53/0	16/4	216
4) M. C.	F	32	1.51	194	12.10		11.76	11.39	12.30	12.01		18.24*	19.01	17.30	91.0	2430	2060	2060	370	0	64/10	34/16	132
5) E. S.	F	5½	0.72	111	11.65		11.48	11.78	11.78	entered but no sample obtained	14.03	20.30*	21.16	16.69	79.0	2400	1540	1540	860	0	116/14	low	179
6) J. P.	M	6	1.00	130*	12.25	12.63	12.30	12.40	12.40	12.20		16.80*	17.35	15.30	88.2	4200	2840	2840	1360	0	38/0	19/15	108
7) S. F.	M	18	1.59	285	23.20		25.20	23.50		25.80		34.60*	35.70	28.30	79.3	5790	1906	1906	3884	0	110/5	22/8	210
Averages	5F–2M														87.7	3740	2501	2501	1239	0	105/11	24/13	249
Normal															96.0	3000	3000	3000	0	0	25/0	25/8	75

(* indicates assumed figures for oxygen consumption in cc./min. or for oxygen content in the pulmonary veins.)

[1] one day after the catheterization studies.

sex distribution was equal and their ages varied from 32 years of age to eight months with an average age of ten years.

Of the thirty-four patients, twenty-two were proven to have valvular stenosis according to the criteria stated above and in twelve the diagnosis was not proven.

TABLE V

Summary of data on catheterization of thirty-four cases of pulmonary valvular stenosis

(A) Proven Cases

NUMBER OF CASES	FORAMEN OVALE	% SAT.	BLOOD FLOW IN CC./MIN./M²			SHUNTS IN CC./MIN./M²		PRESSURES IN MM. HG.			R.V. WORK
			syst.	pul.	eff.	R-L	L-R	R.A.	R.V.	P.A.	
3	closed	95.0	1412	1412	1412	0	0	23/11	171/10	11	242
19	open	76.9	2612	1433	1381	1231	(52)	17/5	135/29	15/9	196
	normal	96.0	3000	3000	3000	0	0	5/0	25/0	25/8	75

(B) Unproven Cases

NUMBER OF CASES	FORAMEN OVALE	% SAT.	BLOOD FLOW IN CC./MIN./M²			SHUNTS IN CC./MIN./M²		PRESSURES IN MM. HG.		R.V. WORK
			syst.	pul.	eff.	R-L	L-R	R.V.	P.A.	
5	closed	96.5	3426	3426	3426	0	0	84/10	23/11	290
7	open	87.7	3740	2501	2501	1239	0	105/11	24/13	249
	normal	96.0	3000	3000	3000	0	0	25/0	25/8	75

(C) All Cases

NUMBER AND SEX OF CASES	FORAMEN OVALE	% SAT.	BLOOD FLOW IN CC./MIN./M²			SHUNTS IN CC./MIN./M²		PRESSURES IN MM. HG.		R.V. WORK
			syst.	pul.	eff.	R-L	L-R	R.V.	P.A.	
8 4 M 4 F	closed	96.0	2670	2670	2670	0	0	117/10	22/10	272
26 13 M 13 F	open	79.8	2900	1710	1670	1230	(40)	127/24	21/12	211
	normal	96.0	3000	3000	3000	0	0	25/0	25/8	75

Nineteen of the twenty-two and seven of the twelve had patency of the foramen ovale.

The following two case reports are representative of patients suffering from pulmonic stenosis with and without patency of the foramen ovale. The first had isolated pulmonic valvular stenosis with closed foramen ovale:—C.B.: This 13 year old boy had a heart murmur since

birth, but had never been cyanotic. He had progressive shortness of breath on exertion and was unable to keep up with other boys. He complained of short periods of dizziness and "blacking out" on exertion.

Physical Examination: There was a definite bulge of the left chest wall. There was no cyanosis or clubbing. The pulse rate was 84 per minute and regular. The blood pressure was 110/86 in the arms. A systolic thrill and a harsh systolic murmur were present over the precordium which were maximal in the third and fourth interspace to the left of the sternum.

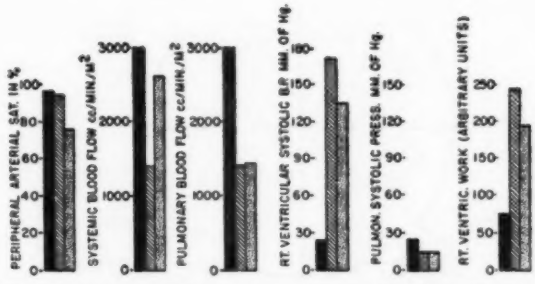
PERIPHERAL ARTERIAL SAT. IN %
SYSTEMIC BLOOD FLOW cc/MIN./M²
PULMONARY BLOOD FLOW cc/MIN./M²
RT. VENTRICULAR SYSTOLIC B.P. MM. OF Hg.
PULMON. SYSTOLIC PRESS. MM. OF Hg.
RT. VENTRIC. WORK (ARBITRARY UNITS)

FIG. 1. Represents a comparison of average normal values with those obtained in proven cases of pulmonic stenosis with and without patent foramen ovale. The solid columns represent normal values, the hatched columns represent average values obtained on patients with closed foramen ovale. The stippled columns represent averages obtained on patients with patent foramen ovale.

On fluoroscopy there was considerable right auricular and ventricular enlargement. The main pulmonary artery was enlarged but pulsated little. The lungs were normal.

The electrical axis of the heart was deviated to the right. The hematocrit was 45.5, the red blood count 5.47 million and the hemoglobin 15.5 grams per cent.

Physiological Studies: The data obtained on catheterization are summarized in Table I and Figure 2. The catheter was introduced into the right auricle, right ventricle and pulmonary artery. There was no significant change in the oxygen content of blood samples obtained from any of these chambers or from the pulmonary artery. Therefore, there was no evidence of a left to right shunt. The peripheral arterial

oxygen saturation was 95.6% demonstrating the absence of a right to left shunt. The systemic, pulmonary artery and effective pulmonary flows were equal and reduced (1710 cc./min./M²). The pressure in the pulmonary artery was 21/9 mm. Hg. When the catheter was pulled back into the right ventricle, the pressure rose sharply to 143/0.

During the standard exercise test (10) the peripheral arterial oxygen saturation did not fall and there was a slight rise in the oxygen consumed per liter of ventilation.

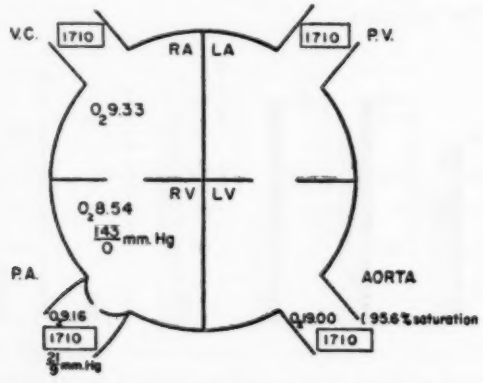

FIG. 2. Outlines the hemodynamic findings on patient C.B. (Table I), in whom the foramen ovale is closed. It may be seen that there is no significant change in the oxygen content of blood samples obtained from any chamber of the heart or the pulmonary artery. The peripheral arterial blood is fully saturated, demonstrating the absence of a right to left shunt.

On the basis of clinical and physiological findings, the diagnosis of isolated valvular pulmonic stenosis with closed foramen ovale was made. Thoracotomy was performed by Dr. Blalock on 11/29/49. The findings at operation confirmed the diagnosis and a pulmonary valvulotomy was performed. The post-operative course was uneventful. The patient was discharged twenty-two days later and since operation has been strikingly improved.

The second patient had isolated valvular stenosis with patent foramen ovale. C. G.: This 12 year old boy first became cyanotic at one year of age. At the age of six he began to tire easily and frequently squatted. He was maintained on digitalis from the age of nine. He was

able to walk a distance of one-half mile to school and back every day and had a high scholastic average. However, he seldom participated in games or sports. During the last two years he had grown progressively worse.

Physical examination: He was a well nourished, distinctly cyanotic child. There was slight clubbing of the fingers and toes. There was no chest deformity. The pulse rate was 80 per minute and regular. The blood pressure was 120/60 in the arms. There was a systolic thrill at the apex and a widely audible systolic murmur which was loudest at

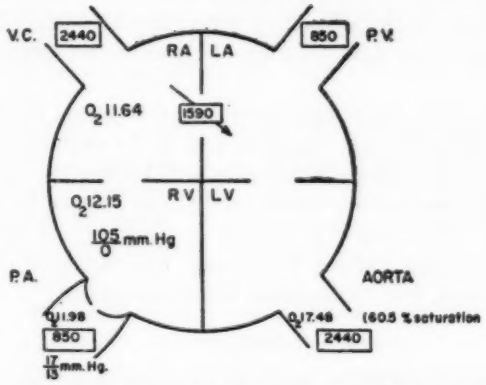

FIG. 3. Illustrates the findings obtained on patient C.G. in whom the foramen ovale is patent. There is no significant difference in the oxygen content of blood samples obtained from the right auricle and ventricle. The peripheral arterial oxygen consumption is significantly reduced, demonstrating the presence of a large right to left shunt.

the apex. The liver was palpable three finger breadths below the costal margin and was pulsatile.

On fluoroscopy there was enlargement of both ventricles. The main pulmonary artery was large but pulsated slightly. The vascular markings in the lungs were normal.

The electrical axis of the heart was normal. The hematocrit was 53, the red blood count 6.52 million and the hemoglobin 15.5 grams percent.

Physiological Findings: The data obtained on catheterization are summarized in Table III and Figure 3. The patient was first cathe-

terized in 1948 but at that time the pulmonary artery was not entered. In March, 1950, he was recatheterized and on this occasion the right auricle, right ventricle and pulmonary artery were successfully intubated. There was no significant difference in the oxygen content of blood samples obtained from each of these sites, demonstrating the absence of a left to right shunt. The peripheral arterial oxygen saturation was 60.5% demonstrating the presence of a large right to left shunt. The systemic blood flow was 2440 cc./min. M^2. The pulmonary artery and effective pulmonary flows were equal (850 cc./min./M^2). The total and overall right to left shunts were 1590 cc./min./M^2 (Fig. 3). The pressure in the pulmonary artery was 17/13 mm. Hg. and on withdrawing into the right ventricle, the pressure rose sharply to 105/0 mm. Hg.

On the basis of clinical and physiological findings, the diagnosis of isolated valvular stenosis with patency of the foramen ovale was made. A pulmonary valvulotomy was performed. During the operation, the heart became progressively weaker and finally stopped beating.

At autopsy there was hypertrophy of the right and left ventricles and the ventricular cavities were small. The pulmonic stenosis was valvular in type, and the foramen ovale was patent.

RESULTS

The findings reported in these two patients show that the oxygen content of blood from the superior vena cava, the right auricle, the right ventricle and the pulmonary artery was identical, regardless of whether or not there was patency of the foramen ovale.

In another patient, (M. B.) the oxygen content of pulmonary artery blood exceeded that of right ventricular blood by 2.9 vol.% (Table III). At autopsy, large systemic collaterals were seen to course from the internal mammary and bronchial arteries to the pulmonary arteries. Mannheimer (11) also found a slight gradient between the oxygen content of right ventricular and pulmonary artery blood in seven cases of pure pulmonic stenosis.

In three of the patients with patent foramen ovale (E. S., J. H. and S. S.) the oxygen content of pulmonary artery blood was lower than that of right ventricular blood (Table II). It is possible that the introduction of a catheter through a severely stenosed pulmonic valve

reduces the systemic flow. As a result the oxygen utilization of the tissues increases and the oxygen content of mixed venous blood declines.

The absence of a gradient between blood from the venae cavae and right auricle is to be expected when the foramen ovale is closed, but even if the foramen is patent there is still no gradient. In the latter case either anatomical or dynamic explanations may be offered. The foramen ovale may be covered on the side of the left auricle by a valve-like structure which allows only right to left shunting. But even in patients in whom this valve was found to be absent at postmortem examination, the overall shunt was entirely from right to left. This was probably the result of a high pressure gradient from the right to left auricle. The possible mechanism of this gradient will be discussed below.

Table I and Fig. 1 illustrate that the oxygen saturation of peripheral arterial blood was normal in patients with valvular pulmonic stenosis without patent foramen ovale. This observation furnishes renewed evidence for the fact that a diminution in pulmonary blood flow alone does not produce arterial unsaturation. Since there was no intracardiac shunt, the systemic, effective and pulmonary artery flows were equal. One might expect that pulmonary stenosis would lead to a reduction in cardiac output. This was the case in C. B., J. D., and C. G. in whom the diagnosis was confirmed at autopsy. In four out of five patients, however, in whom the diagnosis was not confirmed, the cardiac output was normal, or increased (Table I). This may have resulted from increased force of right ventricular contraction when there was only a moderate stenosis of the pulmonic valve. The right ventricular pressure was increased in patients with closed foramen ovale in whom the diagnosis was confirmed (Table I, Fig. 1), the maximal pressure being 198/20. Similar findings were observed by Dow and associates (12). In proven cases with a closed foramen ovale the right auricular systolic pressure was elevated with an average mean of 23 mm. Hg. (Table V). In the proven cases with patent foramen ovale the average right auricular pressure was only 15/7 mm. Hg. (Table V). This finding demonstrates that the inter-auricular communication represents a vent through which blood may escape when the right auricular pressure rises. The mean pulmonary artery pressure in pa-

tients with proven valvular pulmonic stenosis with patent foramen ovale was within the normal range (Fig. 1, Table II). The estimated right ventricular work was well above normal (244 and 154 as compared to normal of 75) (TableI, Fig. 1). As the pulmonary flow in these patients was reduced, it would seem that a proportionately large amount of energy of the right ventricle is dissipated as pressure energy.

In patients in whom the foramen ovale was patent the saturation of peripheral arterial blood was reduced (Table II and III and Fig. 1). In some of these patients the reduction was only slight (93.5%). In others, however, the saturation was below 70%. The lowest saturation observed was 53% (M. B., Table III). The lowered arterial saturation is the result of a right to left shunt through the auricular defect. This right to left shunt can assume considerable magnitude. In patient R. F., it was over 3 liters per square meter of body surface per minute, (Table II).

The presence of a right to left shunt is also responsible for the systemic flow being approximately normal (average 2660 cc./M^2/min., Table II, Fig. 1). For the same reason the average effective and pulmonary artery flows are reduced (1500 cc. in the proven cases (Fig. 1) and 1300 cc. in the unproven cases, Table II and III). No significant left to right shunt was seen in any of the patients with patent foramen ovale, (Tables II and III).

It is probable that the magnitude of the shunt depends upon the gradient between right and left auricular pressure. In the absence of pulmonic stenosis, the shunt through an auricular defect is from left to right, since normaliy, the pressure in the left auricle during most of the cardiac cycle, is greater than that in the right (13, 14). In the presence of pulmonic stenosis, however, the right auricular pressure exceeds that in the left for the whole cardiac cycle, and the shunt is from right to left (14).

Table V illustrates that the right auricular pressure in patients with patent foramen ovale was increased to an average of 15/7. This is considerably higher than the normal mean right auricular pressure of 5 mm. Hg. A possible explanation may be suggested. In patients with valvular pulmonic stenosis, the right ventricular muscle is greatly hypertrophied without dilatation. As a result, the right ventricular

cavity is small. Although the ventricle may empty sufficiently during systole, its limited capacity will lead to a rapid increase in pressure during the phase of rapid ventricular filling. Thus the auricular systolic pressure will rise with equal rapidity during this period. As the tricuspid valve closes, a relatively large residual volume of blood will

TABLE VI

Data obtained from exercise tests in cases with pulmonary valvular stenosis with and without patent foramen ovale

Proven Cases

PATIENT		O_2 CONS./L. OF VENT.		PERIPHERAL SAT.	
		Rest	Exercise	Rest	Exercise
closed foramen ovale	1) C. B.	26.7	29.0	95.6	95.0
	2) C. C.	36.0	42.0	94.0	94.0
	averages	31.4	35.5	94.8	94.5
patent foramen ovale	1) R. H.	27.8	18.0	86.0	63.5
	2) C. S.	24.0	27.2	93.5	78.0
	3) J. M.			83.2	30.0
	4) W. W.	25.6	18.9		
	averages	25.8	21.4	86.4	63.6

Unproven Cases

PATIENT		O_2 CONS./L. OF VENT.		PERIPHERAL SAT.	
		Rest	Exercise	Rest	Exercise
closed foramen ovale	1) R. M. A.	31	39		
patent foramen ovale	1) M. C.	32.6	34.7		

remain in the right auricle during auricular diastole, contributing to an elevation of right auricular diastolic pressure.

The right ventricular pressure in patients with valvular pulmonic stenosis and patent foramen ovale was significantly elevated (Tables II, III, IV, Fig 1). The highest pressure observed was 223/13 mm. Hg. (M. K., Table II). In only three patients was the right ventricular systolic pressure below 100 mm. Hg. (R. F., S. L., Table II) and (C. G., Table III). In the Tetralogy of Fallot the right ventricular pressure

rarely rises above 120 mm. Hg. (2). This difference may be due to the fact that in the latter malformation the ventricular defect prevents such excessive pressures.

As a result of these abnormally high right ventricular pressures the average estimated work of the right ventricle was increased to 3 times the normal value, (Table II and III, Fig. 1). The high degree of right ventricular hypertrophy seen in these patients is an anatomical expression of the increased right ventricular work. The results of the exercise test performed on patients with valvular pulmonic stenosis are illustrated in Table VI. In two out of three patients with patent foramen ovale the oxygen consumption/liter of ventilation fell from rest to exercise. This is in contrast to results obtained in patients with closed foramen ovale, in whom this ratio increased (Table VI). Since the change in respiratory minute volume appears to be the same for both groups, the changes in oxygen consumed must result from differences in the pulmonary blood flow. It is probable that in patients with patent foramen ovale, the right to left shunt increases and deviates blood away from the lung into the systemic circulation. Evidence of this was the significant fall in peripheral oxygen saturation during exercise (Table VI).

DISCUSSION

The results of this investigation demonstrate the following differences in hemodynamics in patients suffering from pulmonic stenosis when the foramen ovale is open or closed. When the foramen ovale is closed, there is no intracardiac shunt, the ratio of effective pulmonary over systemic blood flow is unity and consequently the peripheral oxygen saturation is normal (Fig. 1). On exercise the oxygen consumption per liter of ventilation rises in two out of three patients, indicating their ability to increase the pulmonary blood flow (Table VI). Both right ventricular and auricular pressures are elevated; the latter being a probable sequel to the reduced size of the right ventricular cavity.

When the foramen ovale is open the intracardiac shunt is exclusively right to left, resulting in a reduction of the ratio of effective pulmonary over systemic blood flow and consequently there is peripheral arterial oxygen unsaturation. The shunt is in the same direction whether the foramen ovale is guarded by a valve or not because the right auricular pressure exceeds that of the left during the whole cardiac cycle (14).

During exercise the peripheral arterial oxygen saturation decreases indicating that the interauricular pressure gradient from right to left is even greater (Table VI). There is evidence that the pulmonary blood flow is unable to meet the increased metabolic demands of exercise, possibly due to the combined effects of the pulmonic stenosis and the intracardiac shunt.

The Tetralogy of Fallot resembles pulmonic stenosis with patent foramen ovale in that there is a predominant right to left shunt. However, in the Tetralogy of Fallot there is also usually some left to right admixture resulting from the presence of a high ventricular septal defect and virtual physiological single ventricle (2). The right ventricular pressure in the Tetralogy of Fallot rarely exceeds 120 mm. Hg. and the right auricular pressure is normal. (2).

It is evident that the construction of an artificial ductus arteriosus is not indicated in valvular pulmonic stenosis with closed foramen ovale, because the ratio of effective pulmonary over systemic blood flow is unity. Pulmonary valvulotomy introduced by Brock (1) appears to be the operation of choice if it can be shown that it will ultimately lower the pressure in the right side of the heart. This subject will be discussed in a subsequent report.

In patients with valvular pulmonic stenosis and a patent foramen ovale the construction of an artificial ductus should increase peripheral arterial oxygen saturation because it should increase the ratio of effective pulmonary over systemic blood flow. However, other considerations suggest that here too pulmonary valvulotomy may be the operation of choice. After the construction of an artificial ductus the volume of blood returning to the left auricle is increased. Due to the limited capacity of this chamber the pressure will rise in it and prevent the operation of the interauricular vent mechanism described above. This will result in a further rise in right auricular pressure. Such physiological considerations have been born out by clinical experience which has shown that the creation of an artificial ductus leads to congestive heart failure.

SUMMARY

The physiological findings on thirty-four patients with valvular pulmonic stenosis have been described. Twenty-six had patency of the foramen ovale. In the remainder the foramen ovale was closed.

When the foramen ovale was closed there was no intracardiac shunt and the peripheral arterial oxygen saturation was normal. The oxygen consumed per liter of ventilation rose in two out of three of the patients in whom the exercise test was performed. Both right ventricular and auricular pressures were elevated.

When the foramen ovale was open, the intracardiac shunt was exclusively from right to left resulting in a reduction in peripheral arterial oxygen saturation. This was the case whether the foramen ovale was guarded by a valve or not. The right ventricular and auricular pressures were elevated but not to the same degree as when the foramen ovale was closed.

The reasons for the elevated right auricular pressure were discussed and it was suggested that the elevated pressure may be dependent upon the limited size of the right ventricular cavity.

The alterations in hemodynamics following the construction of an artificial ductus were discussed.

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PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE

XI. A Comparison of the Right and Left Auricular, Capillary and Pulmonary Artery Pressures in Nine Patients with Auricular Septal Defect*

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Hellems and his associates have shown that by wedging a catheter into an end branch of a pulmonary artery, pressures can be recorded which resemble in height those obtained from a pulmonary vein. The pressure thus recorded has been called "pulmonary capillary pressure" because it appears to represent the pressure in the capillary end of the pulmonary vascular tree (1). Lagerloef and Werko (2) studied the variations in pulmonary capillary pressure in patients with cardiac arrhythmias and in patients with mitral stenosis and insufficiency. Recently, Dexter and his associates have compared the pulmonary capillary and the pulmonary artery pressures in normal individuals and in patients with various cardiovascular disorders (3). They have shown that if the pulmonary capillary pressure rises above 25 mm. Hg, the gradient between this pressure and the pulmonary artery pressure increases (3).

An accurate determination of the pulmonary vein pressure in man is of great importance because of the possible role an elevation of this pressure may play in the production of pulmonary edema. Also, in calculation of the resistance of the pulmonary vascular bed, the pressure gradient between pulmonary artery and vein must be known.

It seems, therefore, of interest to reassess this problem by comparing pulmonary capillary, pulmonary artery, pulmonary vein and left

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auricular pressures in man. Previous comparisons between left and right auricular pressures have been made in man by Cournand and Brannon and their associates (9) and in anesthetized dogs by Updyke and co-workers (5).

Pressures were recorded in nine patients with auricular septal defects. The patients varied in age from two to thirty-two years. It may be seen from Table I that two of the patients (K. N. and E. T.), had isolated septal defects. In three (M. E. L., A. J., J. L.,) the defect was combined with a valvular pulmonic stenosis. Two others, (K. C. and V. B.) had mitral stenosis with auricular septal defect (Lutembacher's Syndrome). One, (J. D.) had tricuspid atresia and one (E. G.) had an overriding pulmonary artery with transposition of the aorta. None of the patients were in cardiac failure.

Catheterization was performed according to methods previously described (6). Intracardiac pressures were optically recorded by means of Statham strain gauges and Hathaway oscillograph galvanometers. The zero point for all pressures was approximately 10 cm. anterior to the back with the patient supine. The volume of blood coursing through the intracardiac defect was calculated from formulae previously described (6).

Pulmonary capillary pressures were obtained according to the method of Hellems, Dexter and their associates (1), and the following criteria were used to ascertain that pulmonary capillary pressures were recorded: The tracing obtained from a small branch of the pulmonary artery obstructed by the catheter should be less than that obtained from the pulmonary artery directly, and upon withdrawal of the catheter tip into the lumen of the main pulmonary artery, there should be a sudden increase in pressure.

Simultaneous pressure tracings and electrocardiographic records were not taken, but measurements were recorded in close succession. For comparative purposes it was therefore possible to superimpose such tracings since pressures obtained from both auricules showed characteristic variations during the same cardiac cycle. Both right and left auricular pressure curves usually have the following common features (Fig. 1). A-B) presystolic rise, B-C) fall in pressure due to the descent of the base of the heart, C-D) rise in pressure due to auricular filling, D-A) fall in pressure caused by early ventricular filling, following the

TABLE I

A Comparison of Pressures and Pulmonary Vascular Resistance

In the Patients above the Double Line, Pulmonary Capillary Pressures were recorded.

NAME	AGE	PC	PV		LA	RA	PA	PUL. ARTERIOLAR RESIST.	RV	DIAGNOSIS
			obst.	unobst.						
		mm. Hg	*mm. Hg.*		*mm. Hg.*	*mm. Hg.*	*mm. Hg.*	*mm. Hg/L/min./M²*	*mm. Hg.*	
MEL	8	9.5/2 mean 6	18/11 mean 12	13/8 mean 8.5	9.5/2 mean 6	8/3 mean 4	22/7 mean 12	1.7	130/6	Valvular pul. stenosis patent foramen ovale
EG	4	mean 8		mean 9	mean 7	mean 10	92/80 mean 84	26.5	72/34	Transposition of the aorta, overriding of pul. artery, auricular septal defect
KN	7½	12/6 mean 9	19/13 mean 15		15/7 mean 9	8/0 mean 5	32/15 mean 19	1	36/0	Auricular septal defect
KC	2	22/6 mean 14		24/8 mean 13	18/6 mean 11	18/8 mean 10	34/16 mean 23	1	54/16 36	Auricular septal defect, mitral stenosis
ET	10	22/15 mean 19			19/4 mean 12	10/4 mean 7	34/14 mean 21	.3	46/0	Auricular septal defect
VB	32	30/12 mean 15		21/5 mean 12	21/5 mean 12	23/5 mean 10	82/19 mean 43	4	84/0	Auricular septal defect, mitral stenosis
Average mean press.		12		11.5	9.5	9.4				
JD	13			15/0 mean 5	10/0 mean 3	9/4 mean 6				Tricuspid atresia aur. septal defect
AJ	7				16/10 mean 10.5	21/15 mean 15.5	25/16 mean 19		160/16	Valvular pul. stenosis patent foramen ovale
JL	32				22/3 mean 9	22/8 mean 13			120/10	Valvular pul. stenosis atrial septal defect

opening of the A-V valves. Consequently, *A* represents the beginning of the auricular contraction, *B* the peak of this wave, *C* the beginning of auricular filling and *D* the opening of the A-V valve. The gradient

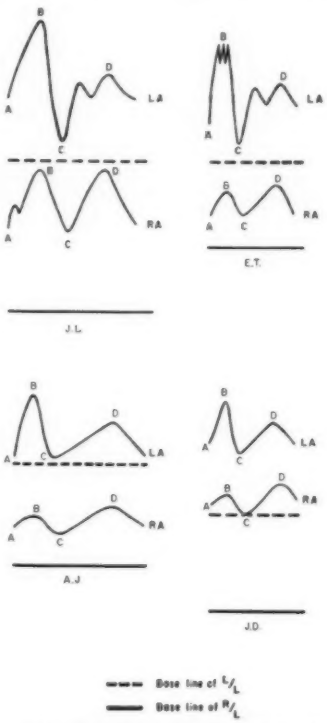

FIG. 1. Represents right and left auricular tracings obtained in 4 patients with auricular septal defects. By relating simultaneous events in the cardiac cycle of both auricles, the tracings could be superimposed on one another. All dimensions are enlarged to 3 times their original values by redrawing them on linear graph paper.

between left and right auricular pressures was determined for points A to D. The gradients between these points were called positive, if the left auricular pressure exceeded that in the right auricle. Conversely, the gradients between the points were called negative, if the right auricular pressure exceeded that in the left.

All pressures were measured in mm. Hg. Mean pressures were calculated by planimetric integration of the area under the pressure curves for at least three cardiac cycles. Since intrathoracic pressures were not recorded, the data do not represent effective pressures.

RESULTS

Comparison of the Configuration of Pulmonary Capillary with Left Auricular Pressures. It was difficult to analyze the shape of the capil-

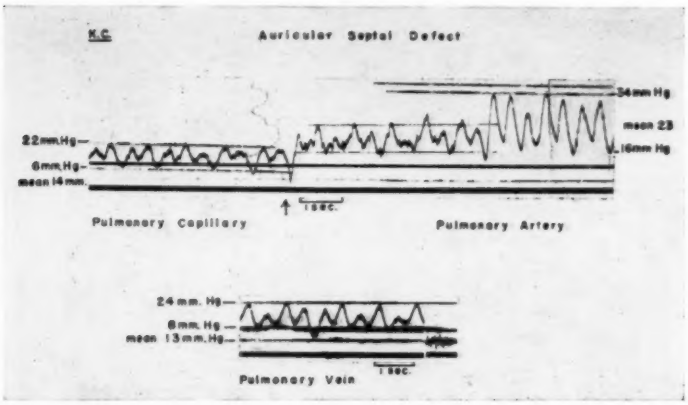

FIG. 2. Shows pulmonary capillary, pulmonary artery and pulmonary vein tracings obtained in patient K. C. with auricular septal defect and mitral stenosis. It may be seen that there is some resemblance between right auricular and pulmonary capillary pressure tracings.

lary tracings because of respiratory variations and of damping caused by obstruction of the catheter tip. It may be seen from Figures 2 to 5 that the shape of the capillary pressure varied from patient to patient and that common features between these tracings were difficult to establish. There was no resemblance between pulmonary capillary and pulmonary artery pressures. This conforms with the findings of other workers (1, 2, 3). Equally, any close resemblance between the configuration of the pulmonary capillary pressure and the tracings recorded from the left auricle was absent. In only one patient (K. C.) was there a pattern of the capillary pressure recognizable. Figure 2 shows that

there was a positive wave with a notched plateau followed by an acute down stroke and a slow elevation. This was followed by a second fall

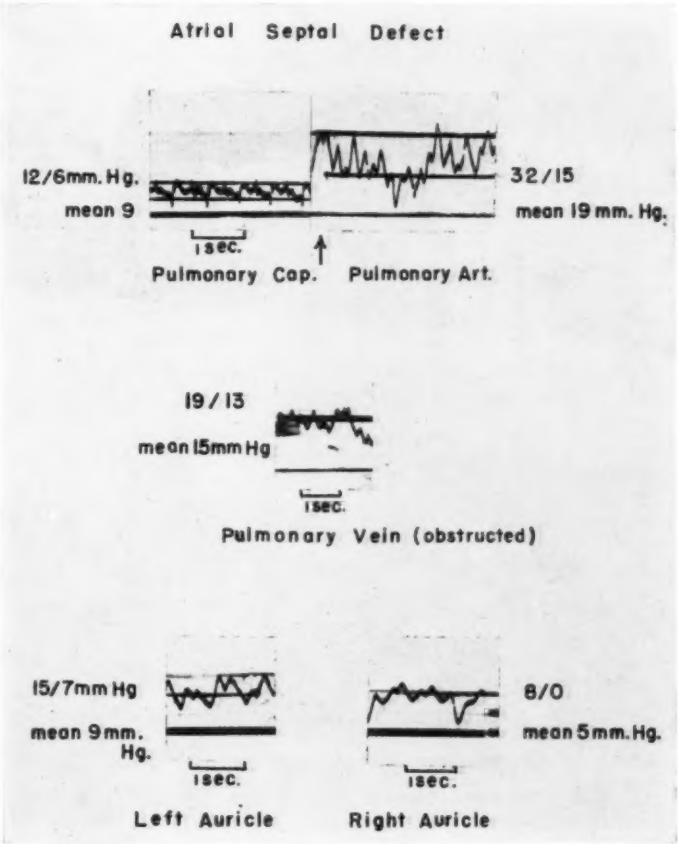

FIG. 3. Illustrates pressure finding obtained in patient K. C. with isolated auricular septal defect.

in pressure which preceeded closely the beginning of the next cycle. This patient had an auricular septal defect with mitral stenosis. Figure 5 shows that in this patient the pulmonary capillary pressure tracing

had some resemblance to that usually recorded from the right auricle. Such a relationship was not seen in any other patient, and is in contrast to the finding of Lagerloef and Werko, who found that the

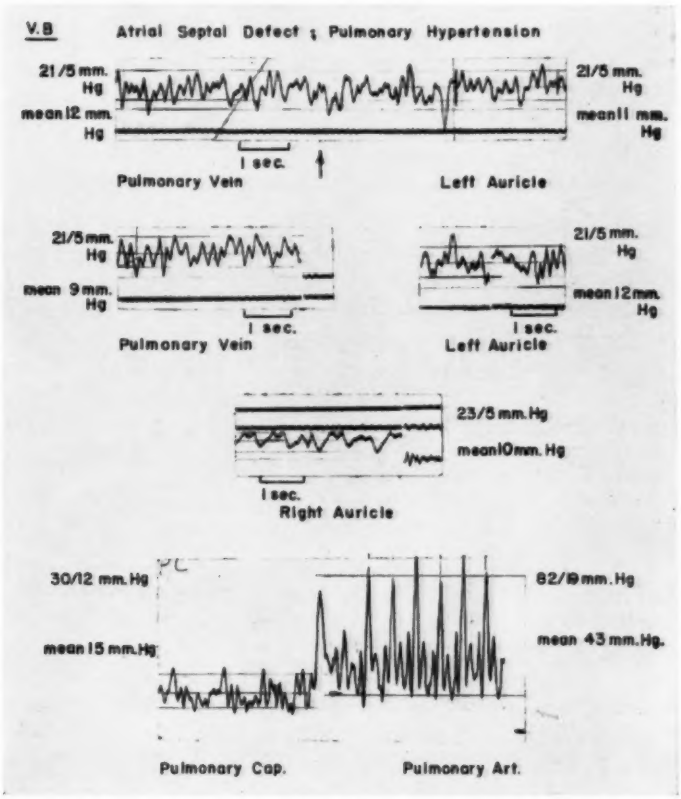

FIG. 4. Represents tracings obtained in patient V. B. with auricular septal defect and mitral stenosis.

pulmonary capillary pressure in different conditions is similar to that recorded from the right auricle (2).

Comparison of the Configuration of Left and Right Auricular Pressure Curves. Left auricular tracings recorded in patients of this series showed

a configuration similar to that previously described by Cournand and his co-workers (4). The left auricular tracings differed from those obtained from the right auricle by a sharper presystolic upstroke, a

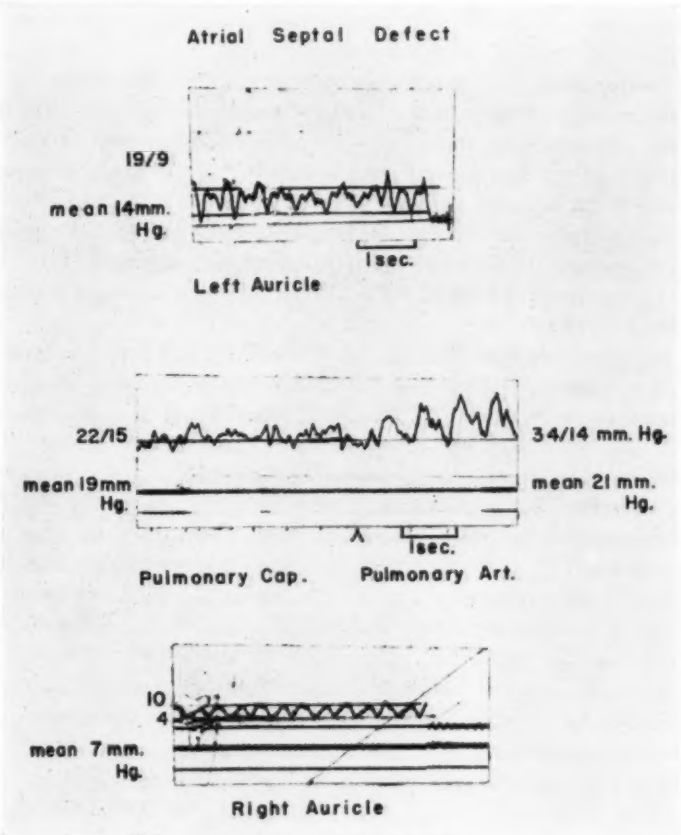

FIG. 5. Represents pressure tracings in patient E. T. with isolated auricular septal defect.

steeper fall due to the descent of the base, and a more rapid second rise during auricular diastole.

Figure 1 illustrates that the left auricular pressure tracings of two

patients (A. J. and J. D.) showed less accentuation of the systolic dip so that the presystolic upstroke appeared to be smoother. The curves during auricular and ventricular filling were rounder. Furthermore, point D which represents the peak of auricular filling just before opening of the mitral valve was only slightly lower than point B which represents the peak of auricular contraction.

Comparison of the Relative Heights of the Pressure Tracings. The relative heights in pulmonary capillary, pulmonary vein, left auricular, right auricular and pulmonary arterial pressure are illustrated in Table I. For comparative purposes only the values of these patients in whom pulmonary capillary pressures were recorded, will be discussed at this point. It may be seen that mean pulmonary capillary pressures ranged from 6 to 19 mm. Hg. with an average of 12. The maximal pressures ranged from 9.5 to 30 mm. Hg., the minimal pressures from 2 to 15 mm. Hg.

In five patients (M. E. L., E. G., K. C., V. B. and J. D.), pulmonary vein pressures were recorded with the catheter tip lying freely in a pulmonary vein, (Table I). In one of these (M. E. L.) the pressures were also recorded with the tip of the catheter wedged deeply into a branch of a pulmonary vein. In another patient (K. N.) the pulmonary vein pressure was recorded from an obstructed vessel only. Table I illustrates that maximal pressures in the *unobstructed* pulmonary vein ranged from 13 to 24 mm. Hg., minimal pressures from 5 to 8 mm. Hg. and mean pressures from 8.5 to 13 mm. Hg. The average mean pressure was 11.5 mm. Hg. In one patient (M. E. L.) obstruction of the pulmonary vein with the catheter tip resulted in a rise in mean pressure of 3.5 mm. (Table I). Similar results were obtained by Hellems and his associates on anesthetized dogs when a pulmonary vein was obstructed (1).

The mean left auricular pressures ranged from 6 to 12 mm. Hg. with an average of 9.5 mm. Hg. The maximal pressure noted at the top of the presystolic peak (point B) ranged from 9.5 to 21 mm. Hg. The minimal pressures measured at the bottom of the systolic dip (point C), ranged from 2 to 7 mm. Hg.

The relationship between pulmonary artery and pulmonary capillary pressures is illustrated in Table I and in Figure 6. It may be seen that the mean pulmonary artery pressure ranged from 12 to 84

mm. Hg., the mean pulmonary capillary pressure from 6 to 19 mm. Hg. There was no direct relationship apparent between the two pressures (Figure 6). For instance, in patient E. G., the mean pulmonary artery pressure was greatly elevated (84 mm. Hg.) but the pulmonary capillary pressure was within normal limits (Fig. 6). On the other hand, in patients E. T. and K. C. the pulmonary artery pressure was normal but the pulmonary capillary pressure was elevated.

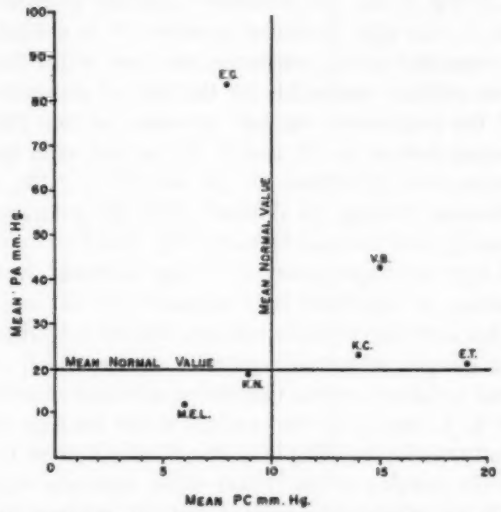

FIG. 6. Shows the relationship between mean pulmonary arterial and mean pulmonary capillary pressures. No direct relationship between the two pressures is noticeable.

Table I shows that in the 6 patients in whom all pressure values were available for comparison, the mean pressure in the right auricle ranged from 4 to 10 mm. Hg. with a mean of 9.4 mm. The maximal pressure, measured at point B, ranged from 8 to 23 mm. Hg. The minimal pressure at point C varied from 0 to 8 mm. Hg.

In the three patients (A. J., J. L., and J. D.) in whom the mean right auricular pressure exceeded left auricular pressures, pulmonic stenosis or atresia of the triscupid valve were present (Table I).

DISCUSSION

From the results reported it is apparent that with possibly one exception, pulmonary capillary pressure tracings are devoid of typical contour, are altered considerably by the phases of respiration and are probably damped. In contrast to the findings of Lagerloef and Werko (2) the pulmonary capillary pressure tracing has no resemblance to the right auricular tracing in the patients of this series. In one patient only (K. C.) (Fig. 2) did the pulmonary capillary pressure bear some resemblance to the right auricular pressure. It is unlikely that the variety of congenital cardiac malformations from which these patients suffered, was entirely responsible for the lack of constant or typical features of the pulmonary capillary pressure; in two patients with auricular septal defects (K. N. and E. T.) as well as in two patients with Lutembacher's Syndrome (V. B. and K. C.) the pulmonary capillary pressure tracings all differed while the pulmonary arterial pressure tracings had constant features (Fig. 2 to 5).

Left and right auricular pressure tracings, however, had a characteristic pattern, as described by Cournand and his associates (4). Generally, left auricular pressure tracings differed from right auricular in having a sharper presystolic upstroke, a steeper fall as the base descends and a sharper second rise during auricular diastole (Fig. 1). In patients A. J., and J. D. the portions of the tracings representing auricular and ventricular filling were smoother and point D, occurring just before the opening of the mitral valve, was only slightly lower than point B occurring at the peak of auricular contraction (Fig. 1).

The average mean pulmonary capillary and pulmonary vein pressures exceed left auricular pressure by 2 mm. Hg. (Table I). A detailed inspection of the data presented in Table I and Figure 7 reveals, however, that in patients in whom the left auricular pressure exceeds 10 mm. Hg. the gradient between mean pulmonary capillary and left auricular pressures increases to 3, 4 and 7 mm. Hg. respectively (K. C., E. T. and V. B.). In contrast, an elevation of the auricular pressure apparently does not result in a disproportionate increase in pulmonary vein pressure (Table I). This finding indicates that the pulmonary capillary pressure does not represent left auricular pressure if the latter is above 10 mm. Hg.

Obstruction of a pulmonary vein by the catheter tip considerably

changes the pressure relationship discussed above. It may be seen from Table I that obstruction of this vessel increases the gradient between pulmonary vein and left auricular pressure to 6 mm. Hg. (M. E. L. and K. N., Table I). Similar observations were reported by Hellems and his associates (1). Obstruction of a pulmonary vein also

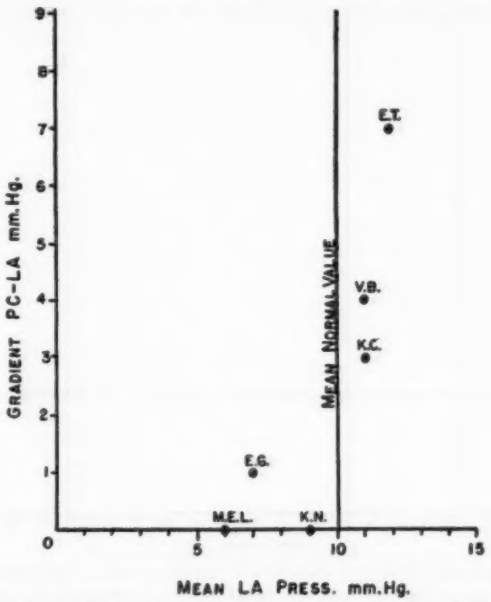

FIG. 7. The relationship between the height of the left auricular pressure and the gradient between pulmonary capillary and left auricular pressure is shown. As the left auricular pressure rises above 10 mm. Hg the difference between pulmonary capillary and left auricular pressure increases.

causes a gradient between the pressure in the obstructed pulmonary vein and pulmonary capillary pressure, (Table I). In 2 patients (M. E. L. and K. N., Table I) this gradient was 6 mm. Hg. (Table I). Hellems and co-workers found similar pressure relationships in anesthetized dogs (1) and felt that "true" pulmonary capillary pressure could be obtained by adding 2 mm. Hg. to the pulmonary capillary pressure or by subtracting 2 mm. Hg. from the pressure obtained in an obstructed pulmonary vein.

Table I and Figure 8 illustrate the absence of any relationship between the pulmonary artery and pulmonary capillary pressure. Either may be elevated independently of the other. Measurements of pulmonary capillary pressure, however, may be of great diagnostic value in patients suffering from pulmonary hypertension. Thus in

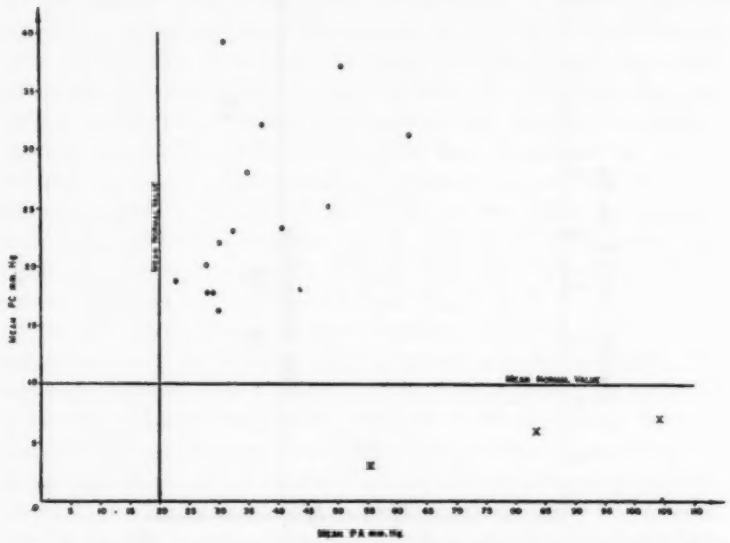

FIG. 8. Illustrates that in patients with mitral stenosis, pulmonary capillary pressures and pulmonary arterial pressures are both elevated. In patients with Eisenmenger's disease and with partial transposition of the great vessels, pulmonary capillary pressures are normal despite pulmonary arterial hypertension. Dots represent values obtained on patients with mitral stenosis, crosses represent values from patients with Eisenmenger's disease or transposition.

two patients with Eisenmenger's and in one with transposition of the aorta and the pulmonary artery overriding both ventricles, pulmonary capillary pressure was normal despite severe pulmonary hypertension (Fig. 8). On the contrary in fifteen patients with mitral valvular disease and pulmonary hypertension the pulmonary capillary pressures were elevated to between 16 and 36 mm. Hg. (Fig 8). Similar findings were obtained by Dexter (3). Pulmonary capillary pressure measure-

ments, then, may help to differentiate between pulmonary hypertension consequent upon pulmonary arteriolar disease, and pulmonary hypertension which is at least partially the result of increased left auricular pressure.

Figure 9 which illustrates the findings in 13 patients with mitral stenosis demonstrates that the gradient between the pulmonary artery

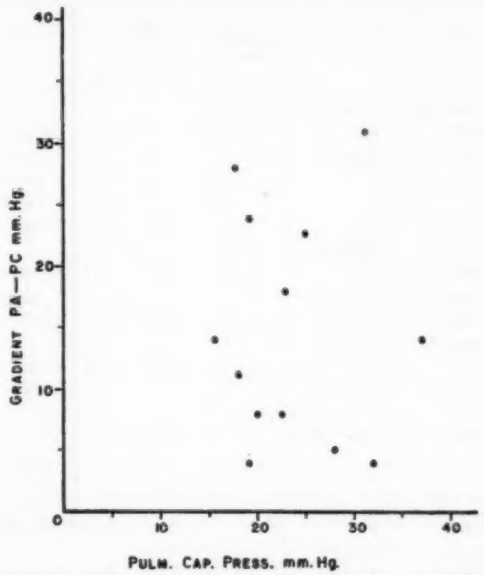

FIG. 9. Illustrates the findings in 13 patients with mitral stenosis. It may be seen that the gradient between pulmonary arterial and capillary pressure does not depend upon the height of the latter.

and pulmonary capillary pressure does not depend upon the height of the latter. Dexter, on the other hand, has found that, if the pulmonary capillary pressure rises above 25 mm. Hg., the pulmonary artery pressure rises disproportionately and as a result the gradient between pulmonary artery and pulmonary capillary pressure increases (3).

The relationship between left and right auricular pressures are illustrated in Table II. It may be seen that in five patients (M. E. L.,

K. N., K. C., E. T., and V. B.) the left auricular pressures were higher than the right with gradients ranging from 2 to 5 mm. Hg. In these patients the intracardiac shunt was directed toward the right. One patient (M. E. L.) had pure pulmonic stenosis with patent foramen

TABLE II

The Relationship of Left and Right Auricular Pressures to the Intracardiac Shunt

NAME	AGE	LA	RA	GRADIENT (MEAN)	SHUNT L/MIN./M²		DIAGNOSIS
					L-R	R-L	
		mm. Hg.	mm. Hg	mm. Hg			
MEL	8	9.5/2 mean 6	8/3 mean 4	+2	0	0	Isolated valvular pulmonic stenosis, patent foramen ovale
KN	7½	15/7 mean 9	8/0 mean 5	+4	4.300	.710	Atrial septal defect
KC	2	18/6 mean 11	18/8 mean 10	+1	5.640	.150	Atrial septal defect, mitral stenosis
ET	10	19/4 mean 12	10/4 mean 7	+5	3.440	.590	Atrial septal defect
VB	32	21/5 mean 11	23/5 mean 10	+1	4.550	.130	Atrial septal defect, mitral stenosis
EG	4	mean 7	mean 10	−3	1.750	4.165	Transposition of the aorta, overriding pul. artery, aur. sep. defect
JD	13	10/0 mean 3	9.4 mean 5	−2	0	1.150	Tricuspid atresia
AJ	7	16/10 mean 10.5	21/15 mean 15.5	−5	0	.640	Isolated valv. pulmonic stenosis, patent foramen ovale
JL	32	22/3 mean 9	22/8 mean 13	−4	.130	1.500	Isolated valv. pulmonic stenosis, atrial septal defect

ovale but no intracardiac shunt. In the four remaining patients of this series, (E. G., J. D., J. L., and A. J.) the mean right auricular pressure exceeded that in the left auricle, with gradients ranging from 3 to 5 mm. Hg. Three of these had a reduction of the pulmonary blood flow due to pulmonic or tricuspid stenosis. One had a partial transposition of the great vessels with an auricular septal defect (7).

The reason for the direction of the intracardiac shunt is the result of the anatomical malformation resulting in the pressure gradients described above. In isolated auricular defect, the left auricular pressure exceeds that in the right due to the limited capacity of the left auricle; therefore the shunt is directed toward the right. If, in addition to the auricular septal defect, a mitral stenosis is present, the pressure gradient between left and right auricles will be even greater and as a result the shunt from left to right will be large (Table II). On the

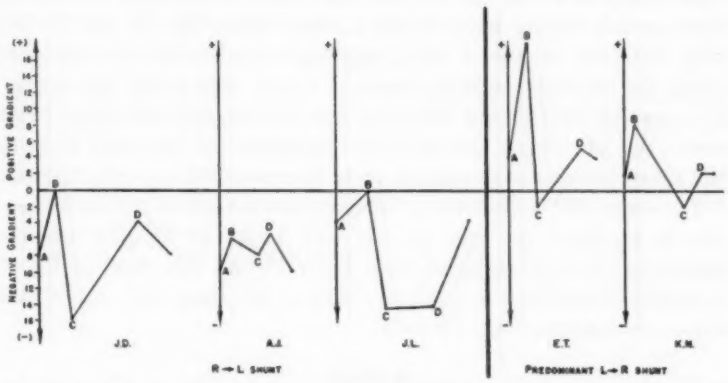

FIG. 10. Shows the gradients between left and right auricular pressures during the various phases of the cardiac cycle (points A to D). The gradient is called negative if the left auricular pressure is less than right auricular and positive if the left auricular pressure is greater than the right auricular.

other hand, in isolated pulmonic stenosis the right auricular pressure is increased, probably as a result of the limited capacity of the right ventricular chamber (8). A similar reason for the elevation of the right auricular pressure may exist in transposition of the aorta with overriding pulmonary artery. Here too, the right auricular pressures are elevated as a result of right ventricular hypertrophy and therefore, reduced capacity of this chamber. In tricuspid atresia the shunt must be directed toward the left to make this condition compatible with life.

In order to investigate the relationship of the phasic pressure changes occurring between the right and left auricles, left and right

auricular pressures obtained in five patients were superimposed on each other according to the method outlined above (Fig. 1). Three of these patients had only a right to left shunt (A. J., J. D., J. L.), while two (E. T. and K. N.) had a predominant left to right shunt (Table II). In the three patients in whom the volume of blood through the auricular septal defect was entirely directed towards the left, the right auricular pressure exceeded that in the left auricle during the whole cardiac cycle (Fig. 10). In patients with a predominant left to right shunt, however, the left auricular pressure exceeded that in the right auricle during most of the cardiac cycle, (K. T. and T. N.) (Fig. 10). Only at point C which represents the beginning of auricular filling did the right auricular pressure exceed that in the left auricle. It is possible that during this short period some right auricular blood enters the left auricle, and may be responsible for the small right to left shunt which was present in these patients (590 cc./min./M^2 and 710 cc./min./M^2 respectively). Similar short periods of reversed direction in gradients for brief periods were found by Opdyke and his associates (5). It is apparent from Table II that this short period of reversal was sufficient to result in a right to left shunt of from 590 and 710 cc./min. respectively (Table II).

SUMMARY

Pulmonary capillary and venous pressures as well as left and right auricular and pulmonary artery pressures were recorded in patients with auricular septal defects.

Considerable variations were found in the shape of the pulmonary capillary pressure while left and right auricular tracings showed characteristic patterns.

The average mean pulmonary capillary and pulmonary vein pressure exceeded left auricular pressure by 2 mm. Hg. In patients, in whom left auricular pressures exceeded 10 mm. Hg., the pulmonary capillary—left auricular pressure gradient increased. Obstruction of the pulmonary vein resulted in a rise in mean pulmonary vein pressure.

No relationship was found to exist between the height of the pulmonary capillary and artery pressure. The gradient between these two pressures was found to be independent on the height of the pulmonary capillary pressure.

The direction of the intracardiac shunt was dependent on the nature of the anatomical malformation.

A comparison of the phasic relation between the right and left auricular pressures revealed that in patients with right to left shunt, the right auricular pressure exceeded that in the left during the whole cardiac cycle. In patients with predominant left to right shunts, the onset of auricular filling was accompanied by a short period during which the right auricular pressure exceeded that in the left. It is probable that this reversal in pressure gradient was sufficient to result in a small right to left shunt through the defect.

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EXPERIMENTAL ALTERATION OF NUCLEAR AND CYTOPLASMIC COMPONENTS OF THE LIVER CELL WITH THIOACETAMIDE

I. Early Onset and Reversibility of Volume Changes of the Nucleolus, Nucleus and Cytoplasm

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Thioacetamide (CH_3CSNH_2) was found to be a very effective agent for the control of orange decay (1) but toxicity studies (2, 3) revealed that doses of the order of 200 milligrams per kilogram produced acute centro-lobular necrosis of the liver in albino rats, while a dietary concentration of 0.032 per cent, amounting to a daily dose of about 25 milligrams per kilogram, induced a type of liver cirrhosis, when fed to rats over a period of several months. This cirrhosis was characterized by a gradually developing diffuse fibrosis and nodularity and an increase in liver weight (Figure A). Enlargement of nuclei and nucleoli, which was often of extreme degree (Figure B), fibroblastic proliferation and hyperplasia of bile ducts, and disc-like eosinophilic intracytoplasmic and intranuclear inclusions, were observed. Further investigation (4) showed that dietary supplements of 0.7 per cent dl-methionine or 0.2 per cent choline chloride did not prevent the development of the lesion, although the livers of the rats given these supplements were smaller at the termination of the experiments than those of the controls given thioacetamide alone, a finding thought to be due to mobilization of fat from the liver cells.

During the investigation of the histogenesis of the liver lesion induced by this dietary concentration it was observed that the earliest morphological effect, well-developed within a few days, was increase in the size of the nucleoli and nuclei of the parenchymal cells. At the same time there was a considerable increase in the weight of the liver. These changes, whose striking magnitude will be shown, were demonstrated after only two days on the diet and occurred in the absence of evidence of any significant degree of cell death or damage, as judged

by the usual criteria. The occurrence of similar changes in routine autopsy material (5), in regenerating rat livers (6, 7, 8, 9, 10) and in the pre-cancerous induction stage of p-dimethylaminoazobenzene (butter yellow) induced liver carcinoma (11, 12) stimulated interest in an investigation of the thioacetamide effect.

FIG. A. Nodular, diffusely fibrotic liver of male albino rat killed after 200 days on stock diet supplemented by 0.032 per cent thioacetamide. Body weight 370 grams, liver weight 21.41 grams (about twice the expected value), thyroid weight 19 milligrams.

Experimental: Seventy to ninety day old male albino rats of the Stanford colony which was derived from the Slonaker strain, were used throughout. To the stock diet, containing 17 per cent protein, thioacetamide was added in the proportion of 32 milligrams to 100 grams of diet. The rats were weighed once or twice weekly and at the start and termination of the experiments. At the chosen time of kill they were dispatched by exsanguination from the aorta under ether anesthesia and the livers weighed to the nearest centigram on a torsion balance. To ensure adequate sampling the livers were then cut into strips about one millimeter thick and every fifth or sixth strip fixed in Bouin's fluid for nuclear measurements, and in other fixatives as required. The strips were blocked in paraffin and sectioned at five microns, several sections being prepared at different levels in the block.

The sections were stained with hematoxylin and eosin, pyronin-methyl green and by the Feulgen technique.

Measurement of Nuclear Volumes: the diameters of the circles intersected by a plane passing through a group of uniform spheres in random distribution in space,

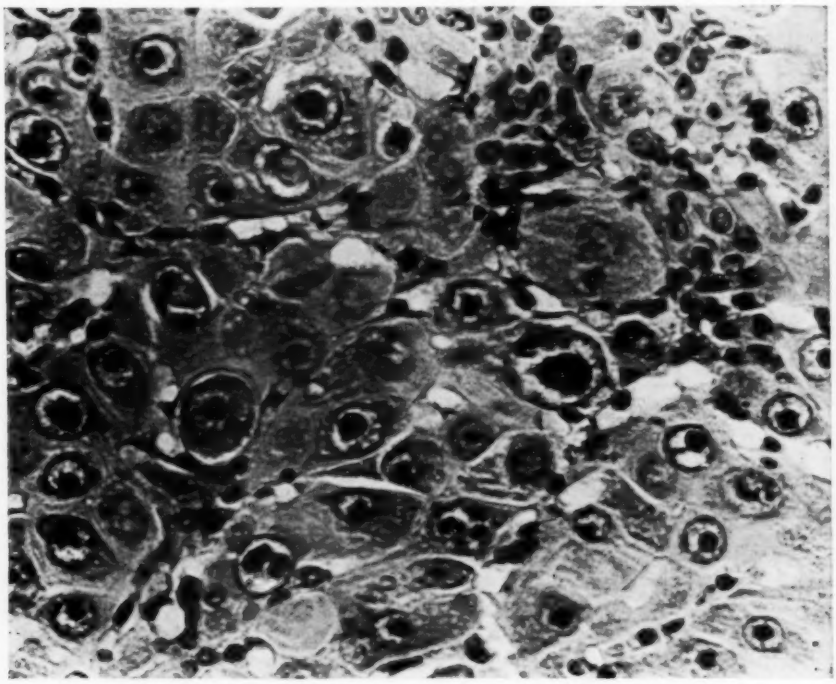

FIG. B. Cytoplasmic, nuclear and nucleolar enlargement in young male albino rat after 78 days on 0.032 per cent thioacetamide. This section is representative of the liver as a whole, except for zones of fibrosis and bile-duct proliferation. The very large *nucleolus* shown has approximately seven times the volume of the predominant type of *nucleus* in the normal rat liver. Hematoxylin and eosin, × 440.

may be arranged in frequency distribution and graphed with the number of nuclei of a given diameter range as the ordinate and the measured diameters as the abscissa. Such a curve would rise from a low value, since some of the spheres would be intersected at less than their maximum diameters, to a peak representing the maximum diameter of the spheres. No diameters would be found beyond this maximum value and the curve would drop off sharply. In the case of spheres

of several distinct volume classes, and the presence also of a slight degree of random variation within each class, curves with as many peaks as volume classes would be generated. The dropoff from the peaks would be more or less gradual. Measurements of liver cell nuclei in tissue sections cut at five microns constitute an approximation of the mathematical situation of the latter type. A further complication, but not a serious one, is introduced by eccentricity of the nuclei. In addition the assumption is made that the shrinkage factor, due to fixation and subsequent processing of the tissue, may be ignored insofar as ratios of volumes are concerned. Although this is probably not strictly true there is reason to believe that it is not a prohibitive factor. It was found that the nuclei could be conveniently and rapidly measured in large numbers with the use of a Scopicon projector unit. The images of the slides were thrown on large sheets of paper and the nuclei drawn in outline and later measured. The procedure was to draw the sharply focused nuclei at a given point on the slide, repeating the process after shifting for several fields and refocusing. Grossly distorted nuclei and nuclei with poorly defined nuclear membranes were not drawn but otherwise the choice was essentially random. The measurements were carried out with the oil immersion objective and the working distance so calibrated that one millimeter on the paper was equivalent to 0.32 microns on the slide. The maximum diameters of the nuclear outlines were measured with a millimeter rule held parallel to the edge of the paper corresponding to the long axis of the slides. An advantage of the method, in addition to its convenience, was that it provided a permanent record from which different measurements could be made. Thus the effect of eccentricity could be tested by repeating the measurements with the rule held at ninety degrees to the long axis (see Fig. 3). From the mean of the measurements on the intersected nuclei, the mean "intersected" nuclear volume was calculated. This is slightly smaller than the true mean nuclear volume, since some of the nuclei are intersected off center by the plane of the section. In practice, however, those nuclei were not drawn since their outlines were blurred. Another way of arriving at a mean nuclear volume which should be quite close to the true value is to estimate, from the height of the peaks on the frequency curve, numbers of nuclei of the different volume classes and calculate a mean volume. Thus for rat #84273 (Fig. 1), a fair estimate would be that 15%, 78% and 7% of the nuclei have volumes of 125, 248 and 500 cubic microns, respectively. The mean nuclear volume would then be 247 cubic microns. A similar estimate on rat #84284 (Fig. 1) yields 238 cubic microns as a mean. Reference to Table I will show that the mean "intersected" nuclear volumes for these two rats are 235 and 231 cubic microns, respectively. Thus the error introduced by estimating nuclear volumes from the nuclei contained in or intersected by the plane of the histological section does not appear to be greater than a few percent.

Nuclear/cytoplasmic ratios: the procedure of Chalkeley (13) was used and the ratio corresponding to 400 randomly chosen nuclear "hits" per liver was calculated. This procedure gives a close approximation to the ratio of the mean volume of the nuclei to the mean volume of the cytoplasm. The mean relative cytoplasmic

volume is equal to the mean intersected nuclear volume multiplied by the reciprocal of the nuclear/cytoplasmic ratio. The mean relative cell volume equals the sum of the mean intersected nuclear volume and the mean relative cytoplasmic volume.

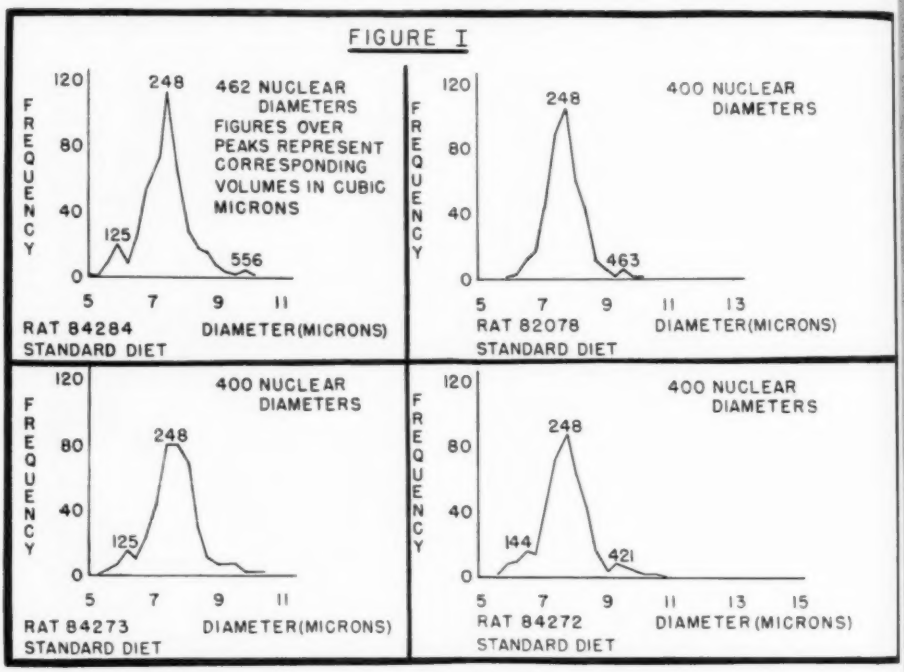

FIG. 1

Discussion of Results: Figure 1 shows four frequency distribution curves of nuclear diameters from control rats. The corresponding nuclear volumes in cubic microns are placed over the peaks which are considered to be significant. The curves of rats #84284 and #84273 show a well defined first peak at 125 cubic microns. The second peak, at 248 cubic microns, is well defined in all four of the rats. The first peak is not visible in the curve for rat #82078 and its position is obscured in rat #84272. The ratio of the nuclear volumes indicated by the first two peaks is close to 1:2. So few of the largest class of nuclei

are present, however, that the third peak does not show up clearly, but it is evident that there are nuclei present which have twice the volume of those giving rise to the second peak. Study of the peaks

TABLE I

RAT #	TREATMENT	A	B	C	D	E	F
84273	Control	235	0.131 ± 0.004	1793	2028	100	94
84284	Control	231	0.133 ± 0.004	1736	1967	97	97
84272	Control	248	0.133 ± 0.005	1864	2112	104	109
83839	Control	227	0.128. ± 0.004	1773	2000	98	98
83812	Killed after two days on thioacetamide	421	0.147 ± 0.005	2863	3284	161	148
83924	Killed after two days on thioacetamide	395	0.150 ± 0.005	2300	2695	132	130
84821	Killed after thirteen days on thioacetamide	508	0.138 ± 0.004	3355	4189	205	129
84820	Killed after thirteen days on thioacetamide	455	0.140 ± 0.004	3250	3705	182	155
84819	Killed nine days after four days on thioacetamide	319	0.132 ± 0.005	2416	2735	134	122
84824	Killed nine days after four days on thioacetamide	289	0.120 ± 0.004	2408	2695	132	112

A. Mean intersected nuclear volume in cubic microns, based on random measurements of 400 nuclear diameters in controls and 800 to 1600 in treated rats.

B. Nuclear/cytoplasmic ratios and standard error, based on 400 random nuclear hits taken in 16 units of 25 hits.

C. Mean relative cytoplasmic volume in cubic microns (nuclear volume multiplied by reciprocal of nuclear/cytoplasmic ratio).

D. Mean relative cell volume in cubic microns.

E. Mean relative cell volume expressed as percent, using mean of four control values as base.

F. Liver weight expressed as percent, using predicted normal value, from equation of Addis and Gray (14) for this colony, as base.

after the administration of thioacetamide gives reason to believe that this third peak is a real entity, as will be shown later. The significance which has been ascribed to these little known volume differences in liver cell nuclei is that the larger nuclei are polyploid, i.e., that they

have integral multiples of the normal chromosome number and that the peaks indicate, respectively, diploid (2N), tetraploid (4N), and octoploid (8N) nuclei. If this interpretation is accepted we are left with the somewhat surprising conclusion that the majority of the parenchymal cells of the rat liver are normally tetraploid. Although spontaneous and induced polyploidy in plants has been the subject of much investigation it has received far less attention in animals. Fankhauser (14) has recently reviewed the zoological aspects of the subject with particular attention to amphibians and salamanders, the only animal species which have been seriously studied. The available data show that there is an approximate doubling of nuclear and cytoplasmic volumes, although many exceptions to the rule are found, when the chromosome number is doubled in a given type of cell. It does not appear that the converse, i.e., that a doubling of nuclear volume in a given type of cell necessarily implies polyploidy, has been shown to hold. Aside from measurements of nuclear volume, however, it is known that polyploid cells may be found in the normal rat liver. Biesele (15) counted the number of chromosomes seen in acetocarmine smear preparations of rat liver cells and found that 54.5% of the metaphase figures were diploid (2N), 40.5% tetraploid (4N) and 5% octoploid (8N), although he counted only 72 metaphase figures to arrive at these percentages. Since they would depend also on frequency of cell division such percentages would not necessarily indicate the proportions of intermitotic nuclei of the three types. There is an obvious disparity between Biesele's figures and the curves for normal rats given in the present paper.

Figure 2 shows three frequency distribution curves of nuclear diameters made on the livers of two rats killed after two days on the diet containing 0.032% thioacetamide. The effect is startling in its magnitude, since if these are truly random samples a majority of the parenchymal cell nuclei have undergone a drastic change in volume. The first peak is not visible. The second, indicating the supposedly tetraploid nuclei, and which in the controls accounted for most of the nuclei, is much lower. In rat #83924 and in one of the two curves for rat #83812, the second peak is at 248 cubic microns, just as in the controls. In the curve constructed from a second group of 800 nuclei in rat #83812, the position of the second peak is indeterminate. The

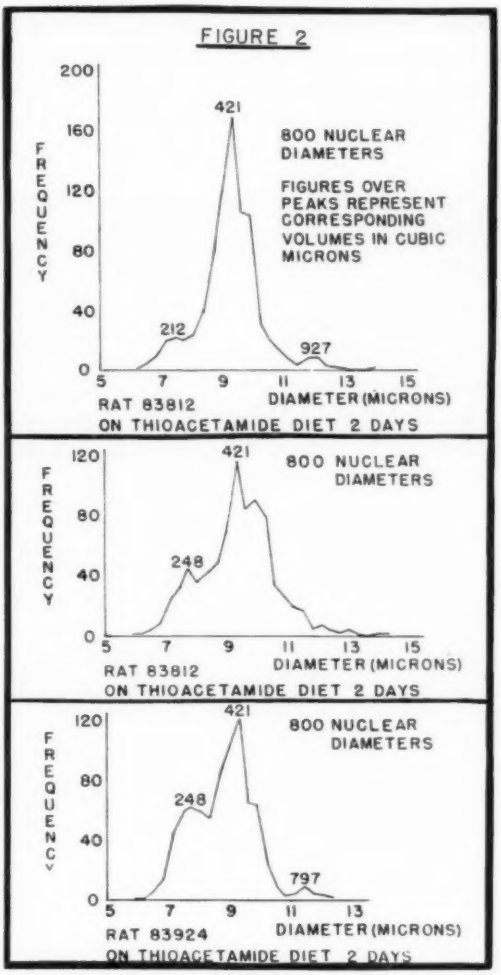

FIG. 2

third peak, whose presence could only be inferred in the controls, is now the highest and the presence of a fourth peak is suggested. This third (with reference to the control curves) peak shows up very clearly at 421 cubic microns. It is difficult to localize the exact position of the

fourth peak but it is evident that there is a tendency for a peak to form in the neighborhood of between 800 and 900 cubic microns. The break in the smooth drop of the curve from the 421 peak is a curious finding. Its persistence in all three curves suggests that it may actually point to a special class of nuclei, but it is impossible to be sure. Table

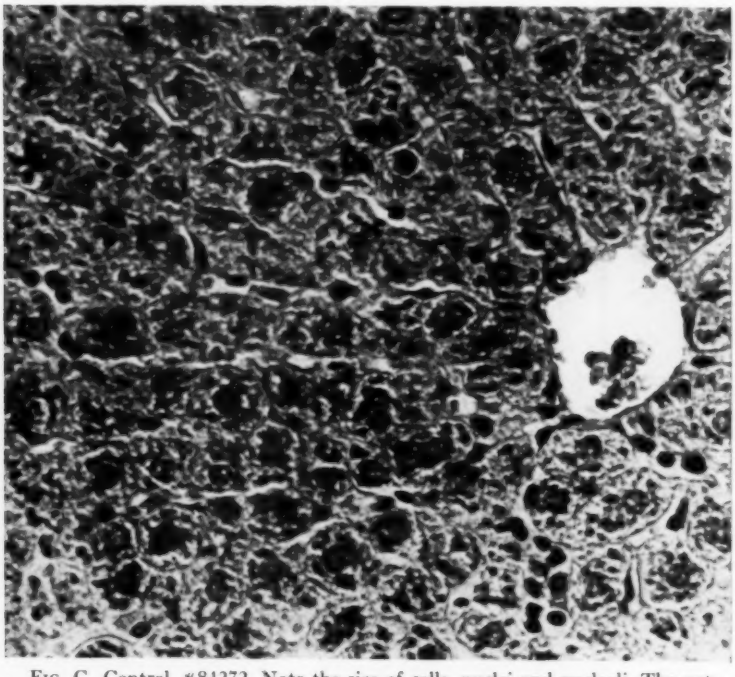

FIG. C. Control #84272. Note the size of cells, nuclei and nucleoli. The cytoplasm contains coarse clumped masses which stain deeply with hematoxylin. Hematoxylin and eosin, × 440.

I shows that the mean intersected nuclear volume has almost doubled, and that the nuclear/cytoplasmic ratio has increased only slightly, which means that enlargement of the entire cell has to a considerable degree kept pace with the nuclear enlargement. Table I shows also that a close correspondence exists between percentage changes in mean cell volume, using the mean of the four controls as a base, and

percentage changes in liver weight, again using the mean of the four controls as a base. The predicted normal values for liver weight were calculated from the equation of Addis and Gray (16) which was derived from data obtained from this rat colony. Since part of the weight of the liver is contributed by the connective tissue framework,

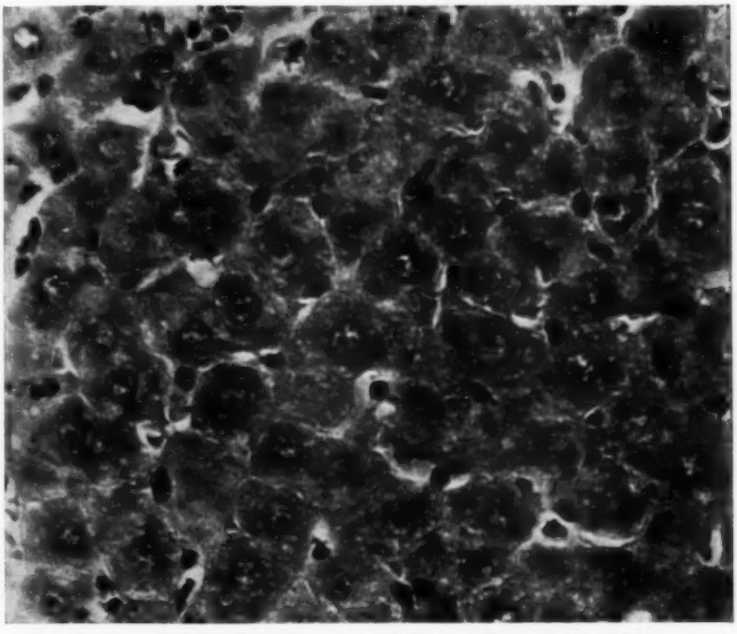

FIG. D. Rat #83924. Two days on stock diet supplemented by 0.032 per cent thioacetamide. The cells as a whole, but in particular the nuclei and nucleoli have enlarged. There are many large single nuclei and the cytoplasm no longer exhibits the clumped basophilia. Hematoxylin and eosin, × 440.

bile-ducts, and blood-vessels, and, since these components probably changed relatively little in bulk, it might be expected that the volume increase of the cells would exceed the weight increase of the whole liver. The specific gravity of the added material would probably vary so little that it seems unlikely that any valid inference may be drawn from these figures as to its chemical composition. Histological studies

showed neither inflammatory infiltration or evidence of edema. As mentioned above, only a minimal degree of cell necrosis was seen, and this not in all of the sections. Sudan IV stains of frozen material showed some of the cells to contain very fine droplets of fat, although this was a more prominent feature of the long term feeding experiments previ-

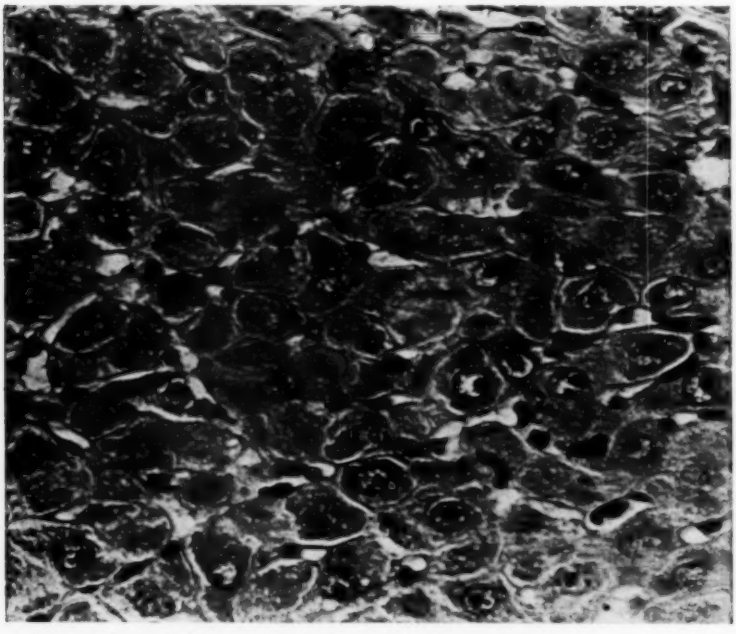

FIG. E. Rat #84821. Thirteen days on 0.032 per cent thioacetamide. Large single nucleoli are more prominent. The eosinophilic, relatively homogeneous cytoplasm contains a few small fat vacuoles. Hematoxylin and eosin, × 440.

ously reported. Figures C, D and E indicate two other remarkable findings in the liver cells of the treated rats, the first being enlargement of the nucleoli and the second, the disappearance of the basophilic masses which are a normal component of the parenchymal liver cell in the rat. The photograph of the control liver (Figure C) shows the tiny nucleoli of the normal nuclei and the lumpy masses in the cytoplasm which stain deeply with basic dyes. In the treated rats the nucleoli

are greatly enlarged and the cytoplasm of most of the cells has become eosinophilic with a fine granularity visible only at high magnification. This diminution of basophilic material in the cytoplasm, more or less homogeneous eosinophilia of the cells and nucleolar enlargement, is still further developed in the rats treated for thirteen days. The nuclei

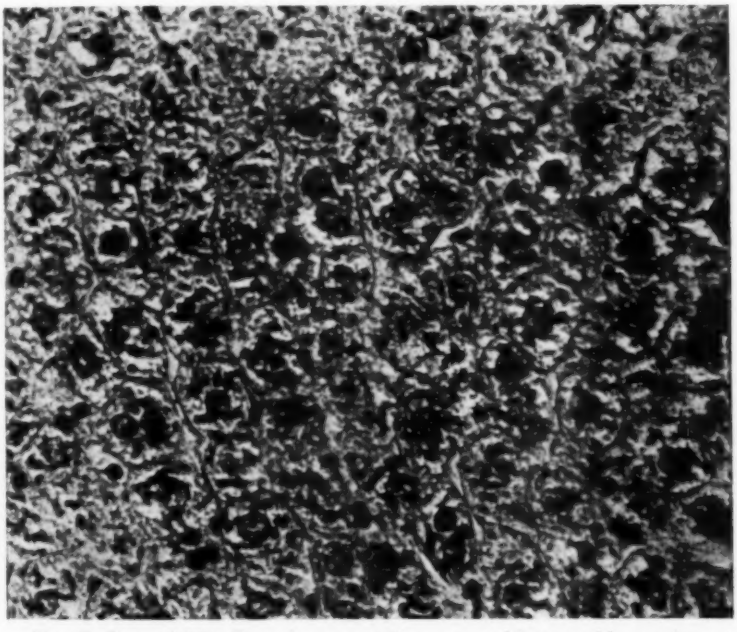

FIG. F. Rat #84824. Four days on 0.032 per cent thioacetamide supplement and killed after nine days "recovery" time on stock diet. A few large nucleoli remain, but the nuclei are again small and the cytoplasm exhibits the clumped basophilia characteristic of the control.

and, to an even greater degree, the nucleoli, have continued to enlarge. Reference to Table I will show that the mean relative nuclear volume almost doubled in two days and more than doubled in thirteen days. These measurements of nuclear volume were based on random sampling of large numbers of nuclei. The cells resemble those of the "hepatoma Type I" described by Edwards and White in the livers of rats treated with p-dimethylaminoazobenzene (17).

The question of the reversibility of the thioacetamide effect was then studied. Two of the animals were placed on the stock diet after four days treatment with thioacetamide. They were killed nine days later. Table I indicates the drop of nuclear and cell volume which must have

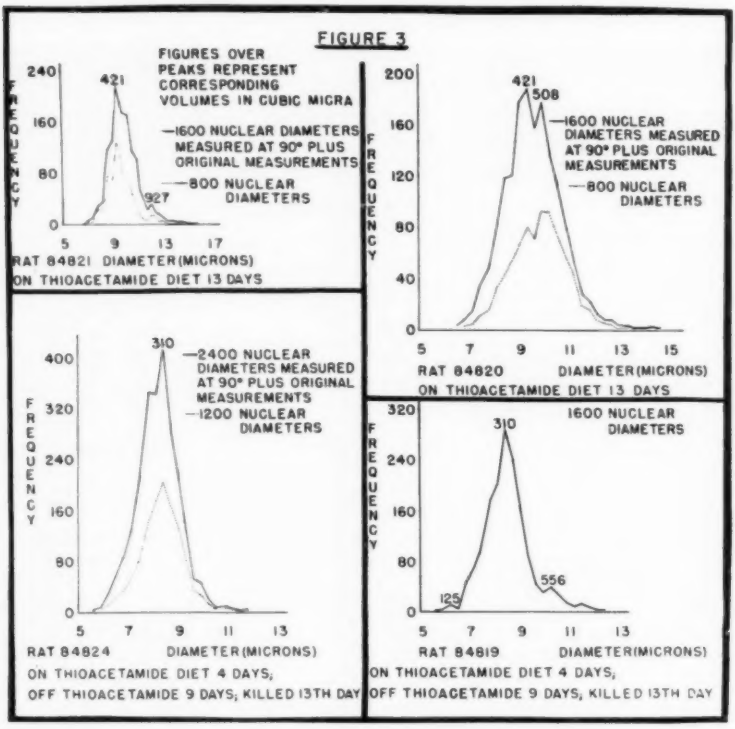
FIGURE 3
FIGURES OVER PEAKS REPRESENT CORRESPONDING VOLUMES IN CUBIC MICRA
—1600 NUCLEAR DIAMETERS MEASURED AT 90° PLUS ORIGINAL MEASUREMENTS
—800 NUCLEAR DIAMETERS
FREQUENCY
DIAMETER (MICRONS)
RAT 84821 ON THIOACETAMIDE DIET 13 DAYS
RAT 84820 ON THIOACETAMIDE DIET 13 DAYS
—2400 NUCLEAR DIAMETERS MEASURED AT 90° PLUS ORIGINAL MEASUREMENTS
—1200 NUCLEAR DIAMETERS
RAT 84824 ON THIOACETAMIDE DIET 4 DAYS, OFF THIOACETAMIDE 9 DAYS, KILLED 13TH DAY
1600 NUCLEAR DIAMETERS
RAT 84819 ON THIOACETAMIDE DIET 4 DAYS, OFF THIOACETAMIDE 9 DAYS, KILLED 13TH DAY

FIG. 3

occurred. Figure F shows that the basophilic masses again pack the cytoplasm and that the nucleoli have receded in size, although an occasional large one persists. Figure 3 shows frequency distribution curves on the two rats treated with thioacetamide for thirteen days, and the two treated for four days and killed after nine days recovery time on the stock diet. In the treated rats the peak at 421 cubic microns is again prominent. The puzzling "subpeak" immediately

following it at 508 cubic microns is in the same position as previously noted in the rats treated for two days. Measurement of the nuclei with the millimeter rule rotated by 90 degrees did not shift the peaks. This is additional evidence that the "subpeak" actually points to a distinct class of nuclei, but again, it is difficult to be certain. A large number of nuclei were measured on the two rats given recovery time on the stock diet. The predominant peak is at 310 cubic microns, which is somewhat greater than the "tetraploid" peak of 248 in the controls. The curve on rat #84819 should be compared with the control #84284 (Figure I). Both show peaks at 125 and 556 cubic microns. Studies on the cells with the Feulgen and pyronin-methyl green techniques are as yet incomplete but the evidence so far indicates that while ribonucleoprotein is accumulating in the enlarging nucleolus it is disappearing from the cytoplasm and that the process is reversible. Opie has shown (12) that ribonucleoprotein is the chief component of these basophilic cytoplasmic bodies and it is of interest that he found the material to be mobilized in rats after several weeks on diets containing 0.060 per cent p-dimethylaminoazobenzene, evidently much more slowly than by thioacetamide.

A point of fundamental importance is the apparent similarity of the nuclear changes which have been observed to follow the operative removal of a large portion of the rat's liver and those induced by thioacetamide. Beams and King (6) studied nuclear volume changes in the livers of rats three days after the surgical removal of approximately two-thirds of this organ. They found bimodal frequency distributions of nuclear volumes of approximately the same character in both their control and hepatectomized animals, but there was a wide lateral spread in the region of the second mode, or peak, in the restoring liver. There were also a number of quite large nuclei beyond the curve proper. They interpreted the larger nuclei as polyploid and suggested that they originated in the following manner: a) after nuclear division by mitosis in a diploid (2N) cell the cytoplasm failed to divide for some unspecified reason, b) the diploid nuclei of the resulting binucleate cell then prepared for mitosis simultaneously but only one spindle formed at metaphase and when division of the chromosomes was complete two tetraploid nuclei resulted, c) if the cytoplasm then divided two tetraploid (4N) cells were formed, but if division was again suppressed

two octoploid (8N) nuclei would be formed at the next mitosis. They found a few nuclei which they interpreted as 16-ploid (16N) in the restoring liver and pointed out that since there was no process by which the number of chromosomes could be reduced, other than by cell death, the restoring liver would come to contain a larger proportion of polyploid cells. Sulkin (7) offered some evidence to support the latter conclusion. The nuclear volume curves which he obtained in his control rats were very like our normal curves, and, using nuclear volume as his sole criterion for the several degrees of ploidy, he calculated that 12% of the nuclei were diploid (2N), 79% tetraploid (4N), 8% octoploid (8N) and 0.4% 16-ploid (16N). For the restored liver, 28 days after the partial hepatectomy, he found 6% diploid (2N), 68% tetraploid (4N), 22% octoploid (8N) and 3.8% 16-ploid (16N). Sulkin found that the larger nuclei were grouped about the central vein and in the restored livers he calculated that about 20% of the nuclei immediately about the central vein were 16-ploid (16N) in contrast to only 6% in the control livers. There is good evidence, however, that the liver cell nuclei may become considerably enlarged in the absence of cell division. Brues, Drury and Brues (8), in one of the earliest quantitative studies of liver regeneration, found that the mass of the residual liver fragment increased by about 50% of its original weight during the first twenty-four hours after the surgical removal of approximately 70% of the organ. They used a technique which allowed for an estimation of the total number of cells in the liver and found no increase in this number during the first twenty-four hours. There was no microscopic evidence of disproportionate increase in other elements of the liver or of intercellular fluids during this period and they concluded that the hepatic cells had increased in size by approximately the same amount. Stowell (9) studied the changes in cell structure and nucleic acid concentration within the first forty-eight hours after the removal of 65% of the liver. At the end of six hours there was an increase in the cytoplasmic, nuclear and nucleolar volumes and an increase in the amount of visible cytoplasmic lipid. The mean nuclear volume had doubled and the mean nucleolar volume quadrupled within twenty-four hours, apparently prior to cell division. Measurements of ultraviolet absorption coefficients on individual cells indicated little change in nucleic acid concentration during this first period of twenty-four

hours, but during the second day there was an increase in nucleic acid concentration in the cytoplasm adjacent to the nucleus and also in the nucleolus. Stowell stated that in normal rat livers the nuclei fell into two groups with a volume ratio of approximately 1:2, but that this evidence of normal polyploidy tended to disappear in the second day of regeneration. Bucher and Glinos (10) found that thirty hours after the removal of approximately 68% of the liver the mean nuclear diameter increased from 7.3 ± 0.48 microns, to 9.0 ± 0.59 microns. This would indicate a nuclear volume increase of 87% above the control value. In the same period of time the portion of liver left in situ increased in weight by about 50% of its original value.

Might not the action of thioacetamide be explained, then, by saying that since large doses produce central necrosis of the liver lobule, the smaller doses used in these experiments have produced necrosis of lesser extent, yet sufficient to be followed by restorative changes in the remaining cells? A few simple considerations show that this explanation must be rejected. There is, in the first place, cytological evidence of the death of only a few cells. Admittedly it is conceivable, even highly probable, that cells may die here and there in the liver and disappear without trace. But the volume changes in the liver cells after thioacetamide treatment are of an order of magnitude as great as, or greater than, those which have been found after operative removal of up to three-quarters of the liver. A minimal degree of focal necrosis throughout the liver could scarcely be expected to produce a response of such order. The enormous nuclei and nucleoli which may be produced by long-continued dietary supplements of thioacetamide have no counterpart in normal regeneration. The large *nucleolus* illustrated in Figure B measures 18 by 12.5 microns, pointing to a volume of approximately seven times that of the predominant type of *nucleus* found in the normal liver. The correlation between the weight increase of the whole liver after thioacetamide and the increase in mean cell volume (Table I) suggests that very few cells succumbed. The change in the cytoplasm involving the disappearance or diminution of the basophilic masses, has not been described in the regenerating liver.

In any case, to refer the changes in the surviving liver cells to the death or removal of other liver cells is a most unsatisfactory mode of explanation which avoids inquiry into the intrinsic casual factors.

There must be some metabolic mechanism, evidently under close organismic control, which maintains and restores, if necessary, the amount of liver tissue present. Of the nature of this controlling system we know precisely nothing. The simplest conception would be that of a humorally mediated process with effects analogous to those exerted over the endocrine glands by hormones of the hypophysis. According to this notion, removal or death of a portion of the liver would lead to a proportionately greater effect on the remaining cells by some hypothetical growth-promoting substance which might be produced in larger amount under such special circumstances as partial hepatectomy. In view of the importance of the hypophysis in general growth processes, it is not surprising that the idea of investigating the regeneration of livers after hepatectomy in hypophysectomized rats occurred to Higgins and Ingle (18). At the end of two weeks they found that the amount of liver regenerated in the hypophysectomized rats was only 27% of that in adequately fed controls. However, this amount was 67% of that regenerated in controls limited to the food intake of the hypophysectomized animals. They concluded that though the hypophysectomy might have interfered slightly with regeneration the experimental situation was complicated by too many factors to permit simple analysis. Histological and cytological studies were not reported on these animals.

The hypothesis is made, therefore, that thioacetamide is effective, not by killing a relatively small number of liver cells and thereby indirectly inducing "compensatory" changes in those remaining, but by acting directly on the liver cell to induce changes which are similar in some respects to those seen after subtotal hepatectomy. These changes consist of a rapid enlargement of the cell as a whole with proportionately greater enlargement of the nucleus and nucleolus, respectively, and rapid mobilization of basophilic material, probably largely ribonucleoprotein, from the cytoplasm. Why are similar changes not seen in other organs or tissues? Although actual measurements were not carried out in tissues other than the liver, previous studies (3) had revealed no significant microscopic alterations elsewhere. The weights of the hearts, kidneys and adrenals did not vary from the predicted values in the present experiments. The lack of effect could be explained either on the basis of a special metabolic characteristic of the parenchymal liver cell, or on the assumption that the liver held or

inactivated a sufficiently large fraction of the ingested thioacetamide. If the latter were the only reason then the effect should be inducible elsewhere by local administration. To investigate this aspect of the problem injections of a 1.0 per cent solution were made directly into the adrenals, kidneys and pancreases of several rats, which were then killed after 48 hours. Nothing which could be construed as a thioacetamide effect on the nuclei could be found when these tissues were studied in comparison with control tissues injected with saline, although enough of the substance was absorbed into the portal circuit to produce definite nuclear changes in the liver. It seems probable, therefore, that the parenchymal liver cell is peculiarly sensitive to thioacetamide. It does not seem likely that the substance failed to penetrate the cell membranes.

Thioacetamide obviously does have profound biological effects on other living cells, since it was remarkably effective in controlling orange decay. Also, Sexton (19) made the very interesting observation that thioacetamide would bring about germination of dormant potatoes and he proposed a possible mode of action. Since it appears that growth-inhibitory ketonic substances are concerned in the regulation of plant growth and seed germination, he suggested that an addition reaction at the double bond by a thiol compound, or compound with thiol function, might be expected to inactivate such inhibitors and thus permit growth. Following this line of thinking, one might suppose that the locus of action of thioacetamide in the liver cell is on some inhibitory enzymatic system, within the nucleus, which controls synthetizing processes. The effect of the thioacetamide might then be to inactivate the inhibitory system and permit less restrained synthesis. The reactions concerned appear to be reversible, at least in the early stages. The maintenance of the nuclear volume ratios, which seems to be fairly definitely shown in the two day feeding experiments, is an extremely interesting and important point. It would indicate that the nuclei tend to enlarge by definite increments, and not in haphazard random fashion. If these volume changes are due to induced polyploidy we must conclude that this is a more reversible phenomenon than heretofore regarded. The same consideration would apply to the question of whether polytene chromosomes were formed, since this too might produce volume increments of the type shown. With regard to the reversibility of the process it does not seem reasonable to suppose

that the larger cells simply died and disappeared from the liver during the nine days after the rats were taken off thioacetamide and placed on the stock diet. Too many cells have been affected for this supposition to have any plausibility.

Nuclear volume alone does not appear to be a sufficient criterion for the assessment of either polyploidy or polyteny, according to Biesele (15, 20). Since there is, theoretically, one nucleolus per chromosome set it might appear that the problem could be settled by counting nucleoli. However, enlarging nucleoli may fuse (14), hence a definitive answer cannot be reached in this manner. In the rats treated for thirteen days there were many nuclei with up to eight nucleoli visible, and, considering the thinness of the sections, probably more present. More frequently seen, however, were cells with single large nucleoli. The problem obviously cannot be solved with the data at hand.

The similarities of the thioacetamide effect to changes occurring in the regenerating liver on the one hand, and those observed in the induction stage of p-dimethylaminoazobene hepatoma on the other, are very interesting. It has already been mentioned that mobilization of the basophilic material in the cytoplasm was described by Opie (12) in the early stages of the induction of butter yellow tumors. Still more interesting is the fact that E. Chiuma (11) of Osake University has recently found that, after twelve days on butter yellow, the volume peaks are maintained but there is a very considerable increase in the number of the larger nuclei. The effect does not appear to have been quantitatively as impressive as that following thioacetamide, since the mean nuclear volume seems to have increased relatively little. Thioacetamide has a profound effect on metabolic processes of the parenchymal liver cell, particularly those involving growth and nucleoprotein metabolism. It would appear that it should be useful as a tool to investigate such processes. The most fruitful time to investigate is that at which it first begins to exert its effect, rather than, as seems often to have been done with the carcinogens, at the end of long term feeding experiments.

SUMMARY

Thioacetamide, in a dietary concentration of 0.032 per cent, has been shown to induce cytological changes in the parenchymal cells of

the rat liver which precede by many months the development of a cirrhotic lesion. These cytological changes, consisting in part of enlargement of the parenchymal cells with relatively greater enlargement of the nuclei and nucleoli, are well-developed within two days. In this period of time the mean nuclear volume is shown to double in value. Studies of relative nuclear volumes, based on measurements of large numbers of nuclear diameters in tissue sections, show the normal liver parenchymal cell nuclei to fall into three classes with a volume ratio of 1:2:4. Between seventy and eighty per cent of the nuclei fall into the second class. The administration of thioacetamide, within two days, leads to a predominance of nuclei of the third class and the appearance of sizable numbers of nuclei of a fourth class having double the volume of the third class. The effect is shown to be at least partially reversible on withdrawal of the thioacetamide from the diet. Disappearance of basophilic material, probably ribonucleoprotein in nature, from the cytoplasm of the affected cells and its reappearance on withdrawal of the thioacetamide accompanies the nuclear changes. The theoretical consequences of these findings, their similarity to changes described in livers regenerating after partial hepatectomy and in the early induction stage of p-dimethylaminoazobenzene hepatoma, and a possible mechanism through which the thioacetamide exerts its effect, are discussed.

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ONE STAGE RESECTION OF ENTIRE COLON AND RECTUM FOR ULCERATIVE COLITIS AND POLYPOID ADENOMATOSIS*

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The field of large bowel surgery remained virtually untouched until the last quarter of the 19th century. The technical difficulties of bowel suture and the fear of peritonitis combined to discourage the ventures of surgeons in this direction.

In 1710 Littre, the French anatomist, discussing a case of congenital obstruction of the rectum before the Royal Academy of Sciences in Paris, not only indicated an application for anastomosis of the bowel, but made the first clear recommendation of colostomy that is recorded (1). The correspondent of the Royal Academy concluded his report as follows: "Monsieur Littre, who wished to render his observation useful, imagined and proposed an extremely delicate surgical operation for cases in which one might recognize a similar conformation. It would be necessary to make an incision in the belly and sew together the two parts of the intestine after having incised them, or at least, to make the superior portion of the intestine come out on the belly wall where one would never close it, and where it would have the function of an anus. To this nimble idea surgeons may imagine for themselves the details which we omit. It is often sufficient to know in the large, that a thing may be possible and not to despair of it at first sight." Despite this suggestion, over a century elapsed before the appearance of a published report of a successful colon anastomosis.

In 1844, the French Academy of Medicine received a communication from Reybard of Lyon concerning a successful resection and anastomosis of the sigmoid colon, which he claimed to have performed eleven years before, in 1833 (2). The incredulous Academy appointed a commission of investigation which submitted its report on July 30,

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1844. Described were Reybard's account of the operation and the animal experiments which he performed to convince the commission. His patient had been a twenty-eight year old man who had suffered pain and intermittent obstruction for six months. A tumor was palpable in the left lower quadrant. Reybard, operating with the presumptive diagnosis of carcinoma of the sigmoid, resected three inches of intestine, sutured mesentery, ligated vessels and performed an end-to-end anastomosis. The tumor was hard and white, but the specimen had been lost in the eleven intervening years. The wound separated, but by the thirty-eighth day after operation, it had healed and bowel movements were natural. The patient succumbed to recurrence ten months later and no autopsy was performed.

For the investigating commission Reybard performed seven resections of the colon in dogs, with primary anastomoses. In every instance there was failure of primary healing and four of the animals died. The outcome of the matter was that Reybard's report was not accepted by the Academy for want of sufficient scientific corroboration. However, the report of the commission remains in the record, and it is significant that the commission gave credence to Reybard's account of the resection and survival of the patient. The first successful resection of the large bowel on record is therefore probably that of Reybard.

No further communication appeared regarding colon resection until 1855 when Thiersch reported losing a patient from a fulminant peritonitis immediately after resection of a segment of colon for acute obstruction due to malignancy. Gross fecal contamination of the peritoneal cavity occurred during the procedure so that Thiersch fashioned a proximal colostomy and then performed an end-to-end anastomosis (3). In 1879 Billroth reported a similar failure with an attempted resection and colostomy (4).

In that year Gussenbauer, Professor of Surgery at the University of Prague, was called to Berlin in consultation by a young Hamburg surgeon named Martini. A forty-nine year old man had presented himself to Martini with symptoms of increasing obstruction and with a movable tumor in the region of the sigmoid. Wilms had already seen the patient and advised resection. Gussenbauer who had had two unsuccessful resections of his own, also advised resection and returned to

Hamburg with patient and surgeon to assist in the operation. Gussenbauer had previously recorded his opinion that in such tumors an adequate resection precluded the possibility of anastomosis while a resection limited enough to permit anastomosis would surely be followed by local recurrence and malignant stenosis. Martini resected the bowel, affected glands, and mesentery, formed a colostomy and closed the distal segment. The patient survived the operation, which was performed November 9, 1879 but Martini died soon afterwards and Gussenbauer reported the case—the second recorded instance of survival following colon resection (5).

By 1882 sufficient interest had been aroused in the possibility and feasibility of colon resection so that Mr. John Marshall presented before the University College Hospital in London, two clinical lectures on "Colectomy," describing the operative technique and summarizing the experiences with the procedure to that time. He discussed seven collected cases, including his own. In four the operation had succeeded in prolonging life for several months, while the other three patients died of the operation (6).

In 1886, four years later, Robert F. Weir of New York reported thirty-five collected cases of intestinal resection for malignant growth, the last of which was his own case, the first success of its kind in this country. An analysis of these cases reveals that sixteen patients recovered, including Weir's, leaving an immediate mortality of 54%. Ten of the sixteen survivors had had primary anastomoses. Peritonitis accounted for most of the deaths, and in the group who survived, wound infections and temporary fecal fistulae occurred regularly (7). It is of interest to note that there is included in the group of immediate failures, an instance in which Schede, operating in 1879, found extensive malignancy. He exteriorized the bowel, resected it, and left both ends attached to the abdominal wall—an unwitting demonstration of the feasibility of staged resections.

During this period most resections were still being carried out for cancer, and the resection was generally limited to the involved segment of bowel. However, the first instance of colon resection sufficiently extensive to be designated a total colectomy was an operation performed upon a patient suffering repeated hemorrhage from polypoid adenomatosis of the colon. On June 15, 1900, Dr. Howard Lilienthal

of New York carried out a resection of terminal ileum, ascending, transverse, descending, and proximal sigmoid colon in a 21 year old girl, as the second stage of a two stage procedure. Three months before, an end-to-end ileo-sigmoidostomy had been performed. The result was most gratifying and the procedure was reported in detail (8). Lilienthal presented this patient, with pardonable pride, before the New York Surgical Society two and one-half years later (9).

The early decades of the century were marked by a sharp reduction in operative mortality, due largely to the increase in the general use of multiple stage operations for resection of the colon. The use of Paul's principle of exteriorization had enabled von Mikulicz to reduce his operative mortality markedly. While resection with primary anastomosis caused him to lose over 40% of his patients, in staged resections his series showed a mortality of only 12.5% (10).

Concurrently, efforts were extended toward combatting post-operative infection. Mechanical ingenuity was invoked, and the popular Murphy button brought intestinal surgery within the competence of most experienced surgeons. The researches of Halsted and Senn in the techniques of reestablishment of intestinal continuity led to the development of a variety of methods for direct anastomosis of bowel with greatly reduced danger of leakage.

Perhaps the most striking individual example of surgical virtuosity brought to bear in this sphere was the achievement of Sir W. Arbuthnot Lane. In his misguided onslaught upon "auto-intoxication" he operated, it is true, upon essentially normal colons. Nevertheless, in a period when antibiotics and freely available transfusions were unheard of, he was able to perform with success one stage colectomy and ileo-sigmoidostomy. In a mutual presentation with Lane in London in 1913, Professor William Bainbridge of N. Y. discussed the fifty-two colectomies Lane had performed from May 1909 to October 1913. There had been only five deaths in the hospital in the entire series, a mortality of 10% (11).

The formal presentation of staged resection of the whole colon and rectum as the surgical treatment for recognized organic disease of the large bowel came in 1931. In that year, Dr. Fred Rankin reported to the American Surgical Association on six cases in which he had performed staged total colectomy and rectal resection in the treatment of polypoid adenomatosis of the colon and chronic ulcerative colitis

(12, 13). The discussants commented upon the wisdom and safety of staged procedures, and it may be said that it is still common practice in most clinics to perform total colectomy in two or more stages. Nevertheless, a method for one stage "aseptic" total colectomy and rectal resection was described in 1940 by Dr. D. Philip Mac Guire of New York (14). No clinical experience was cited.

The powerful adjuvants to surgery which have come into popular usage today are responsible for mortality rates of 2% in clinics where as recently as 1935 mortalities of 10% for colon resection were reported with satisfaction. The value of intestinal decompression was emphasized and clarified by Wangensteen (16), and its use extended generally by the adoption of indwelling intestinal tubes introduced in 1934 by Miller and Abbott (17). The report of Firor and Jonas in 1941 on the benefits of pre-operative preparation with sulfanilylguanidine (18) was followed in the same year by the introduction of succinlysulfathiazole by Poth and Knotts (19). Within a few years, chemical preparation of the colon for surgery had become routine practice. The institution of blood banks in 1937–1939 increased the availability and utilization of whole blood. The ensuant change in attitude toward blood transfusion has been of prime importance in the successful accomplishment of massive surgical procedures. The antibiotics, reinforcing the sulfonamides, have minimized the danger from infection and justified a heightened aggressiveness in the surgical attack upon disease of the large bowel.

In two chronic non-malignant conditions it may be necessary to remove the entire colon, rectum, and anus. In polypoid adenomatosis of the colon, it is generally agreed that cancer of the rectum or colon will eventually supervene in all cases (20, 21, 22). Total colectomy and resection of the rectal mucosa guarantees patients with this disease freedom from the possibility of cancer of the colon. Any procedure which condones less than complete removal of the colon and rectum denies this guarantee. The most frequent compromise in this regard is the failure to resect the rectum when the colon is removed, leaving behind the very organ in which malignancy is most prone to occur. Our preference is for total colectomy with resection of rectal mucosa and submucosa and the establishment of an anal ileostomy rather than an abdominal ileostomy (23).

In chronic ulcerative colitis which is well established, ileostomy offers

the best hope of arresting the disease and saving the patient. In a small group of cases it may subsequently be possible to close the ileostomy and to restore the continuity of the alimentary canal. In the largest number of cases the disease is brought under control, the patient gains in weight, but the colon becomes hopelessly scarred and contracted. In less fortunate cases, even this is not achieved, and discharge of blood and pus continues and the patient remains ill. In this group total colectomy is required for the relief of symptoms, and the restoration of health. Recently it has become apparent that even those with apparently quiescent disease in the retained colon stand in some danger—principally of developing cancer. There is a growing feeling that with the passage of time, in a patient with ulcerative colitis, however dormant, this threat is of sufficient gravity to influence the decision to remove a diseased and useless organ (24, 25).

A number of authors have resected all of the colon but the rectum for ulcerative colitis and anastomosed the ileum to the rectum or recto-sigmoid. Wangensteen (26) has performed a total colectomy, rectal excision and ileal pull through to the anus.

It is a commonplace that patients with ulcerative colitis experience a great improvement physically and mentally when total colectomy is finally performed. Since the rectum is usually the most diseased area, and a frequent source of abscesses and fistulae, resection of the rectum is added to total colectomy. When the condition of the tissues of the anus and sphincter is good, and the patient has sufficient determination to face what may be a protracted period of discomfort, anal ileostomy may complement colectomy in this condition as well.

The experience reported below substantiates the feeling that there is now seldom any need to subject patients to multiple stage procedures for total colectomy. Most patients with ulcerative colitis will have had ileostomies performed before the decision is made to perform colectomy, but even in this regard there is a recent trend towards subtotal colectomy at the time of ileostomy (27, 28). In case #6 J. R., Dr. E. S. Stafford performed colectomy and abdomino-perineal resection of the rectum at the time of ileostomy. Further support is lent to the feasibility of complete one-stage resection by the four cases in which resection was complemented by the fashioning of an anal ileostomy, a procedure more time consuming than anal excision and abdominal ileostomy.

TECHNIQUE

A five to seven day course of succinylsulfathiazole or sulfaphthalidine therapy is administered in conjunction with a low residue diet in preparing these patients for operation. If an ileostomy exists, the colon is irrigated daily with a 10% suspension of the respective sulfonamide, supplemented by the daily instillation into the distal loop of five grams of the drug in one ounce of water. A single lumen intestinal decompression tube (Cantor) is passed 48 hours before operation and permitted to advance well down into the ileum. Pencillin and dihydrostreptomycin administration is begun the night preceding operation.

Several of the patients have been operated upon in the combined lithotomy-Trendelenburg position. To those familar with synchronous abdomino-perineal surgery, the advantages of this position are well known. Inhalation anaesthesia,—nitrous oxide, oxygen, ether,—has been employed, often with intravenous pentothal sodium induction. The abdominal phase of the operation has been carried out through a lower midline incision.*

After dividing the terminal ileum, or, in the case of a pre-existing ileostomy, freeing the mucous fistula (fig. 1), the lateral peritoneal reflection of the right colon is incised. The avascular suspension of the hepatic flexure is released and the mesentery of the right colon and transverse colon divided and transfixed (fig. 2). It is convenient to divide and ligate the gastro-colic ligament and remove the omentum with the colon (fig. 3). If the left peritoneal reflection is next incised and the left colon mobilized, the splenic flexure may be drawn down and its avascular suspension severed (fig. 4 a & b). The lower midline incision permits adequate exposure to accomplish this without difficulty. The small bowel, telescoped on the indwelling tube, is packed to the left while cecum and ascending colon are being freed, and to the right when the descending colon is attacked. Trendelenburg position should not be employed until the sigmoid is reached as the small intestine will otherwise be found constantly in the way. The mesentery of the left colon is transfixed and the rectum mobilized as in any abdomino-perineal resection (fig. 5). One may take the convenient and safer course of dissecting closer to the bowel than in the ordinary Miles

* In case 6, J. R. a transverse upper abdominal incision was used.

operation since this procedure is not performed for malignant disease. The rectum is divided at a convenient point, ligated, covered, and the

FIG. 1. The peritoneal cavity is entered through a lower midline incision. The ileostomy is plugged with a gauze sponge and the mucous fistula occluded with a tie. The fistula is then freed from the abdominal wall by sharp dissection. A finger introduced against the peritoneum guides the dissection.

peritoneal floor reconstructed. The abdominal wall is closed in layers, and an ileostomy established if necessary.

The perineal phase of the procedure in suitable cases may be carried out according to the special technique employed for performing anal

FIG. 2. The peritoneal reflection of the cecum and ascending colon is divided and the right colon and terminal ileum delivered. The mesentery is divided and transfixed. The defect in the abdominal wall left by excision of the mucous fistula is sutured.

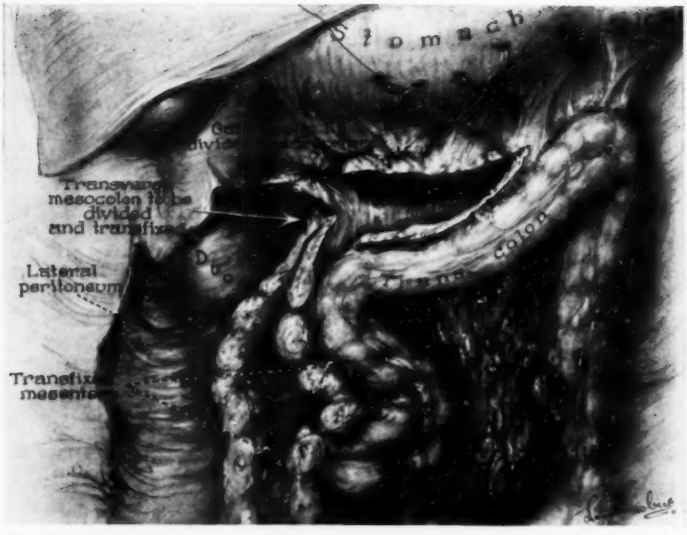


FIG. 3. The hepatic flexure is freed and the gastro-colic ligament divided and transfixed. The transverse mesocolon is separately divided and suture ligated. Up to this point the small intestine is packed away to the left. The presence of an indwelling intestinal tube keeps the small bowel collapsed, compact and easily managed.

a b

FIG. 4. Mobilization of the Splenic Flexure

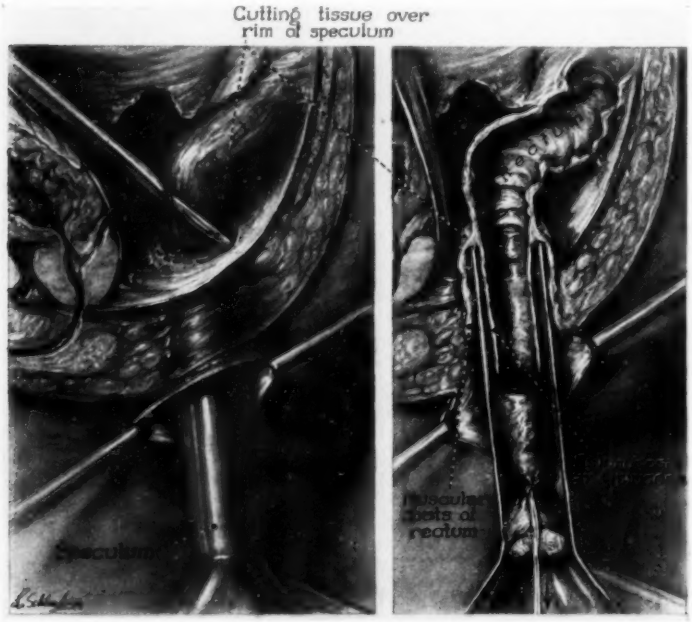
a. The peritoneal reflection of the descending colon is divided and the descending colon retracted medially.

b. Traction is made downward and medially on the two limbs of the splenic flexure bringing the splenic flexure down into the wound. The avascular peritoneal attachments between colon and spleen, placed on stretch, are severed. The small intestine now packed off to the right, is out of the way.

FIG. 5. The patient is in the Trendelenburg position and the small bowel packed cephalad. The colon has been completely mobilized. The mesentery has been suture ligated, and the left ureter visualized and protected as the mesosigmoid is divided. The rectosigmoid is usually divided between clamps at a convenient level, and the colon removed. If the abdominal wound is left open while the perineal dissection is completed there is no need to divide the rectum, and the entire specimen may be removed intact. If the bowel is divided at this point, the end of the distal segment is covered and the pelvic peritoneum repaired. If the bowel is not now divided the peritoneal floor is repaired after completion of the perineal phase of the operation. No effort is made to reperitonealize the gutters.

ileostomy, (fig. 6), or in the routine manner practiced in resection for carcinoma of the rectum. However, here again, since there is no malignancy, the mass of tissue excised may be small, and the levators severed so close to the rectum as to permit their suture as the deepest layer in

the perineal closure (fig. 7). A rubber tissue drain in the pelvis permits drainage from the perineum.



a b

FIG. 6. Anal Ileostomy

The patient is in the combined lithotomy-Trendelenburg position.

a. The rectal mucosa and submucosa are dissected from the rectal muscularis to a level above the levators. A speculum is introduced over this cuff.

b. An incision is made on the edge of the speculum, freeing the upper rectum and the lower rectal mucosa from the tube of rectal muscularis and sphincter.

This procedure has required some three and one-half hours of operating time. In none of the patients presented in this series has there been any significant change in the patient's vital signs or any untoward incident during operation. The continuous infusion of 1500 to 2000 c.c. of blood during operation has been held to be largely responsible for this maintenance of physiological equilibrium.

Suction has been applied to the Cantor tube for 2 to 4 days postoperatively, until the passage of gas and stool per ileostomy has assured

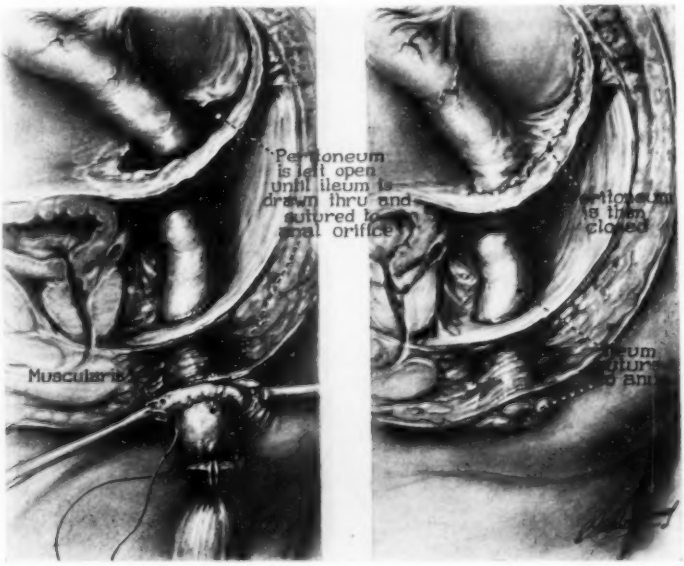


FIG. 6

c. The ileum has been drawn through the cylinder of rectal musculature and the ileal serosa is tacked to the rectal muscle.

d. Two additional rows of sutures are placed, (1) between ileum and external sphincter and (2) between the end of ileum and the anal skin. The pelvic peritoneum is simultaneously repaired from above. Usually several loops of ileum lie beneath the peritoneum.

the return of intestinal motility. Progessive feeding is then begun. Until this time the patients are maintained on intravenous crystalloids, vitamins, and blood as indicated. A prophylactic course of penicillin and dihydrostreptomycin is given routinely. The urethral catheter is removed in 24 hours and the patient encouraged to walk. The perineal drain is loosened on the third day and withdrawn on the 5th or 6th postoperative day.

CASE REPORTS

#1 E. S., JHH #273608. This patient, a 36 year old housewife, had an eleven year history of ulcerative colitis with bloody diarrhoea and severe weight loss. Her

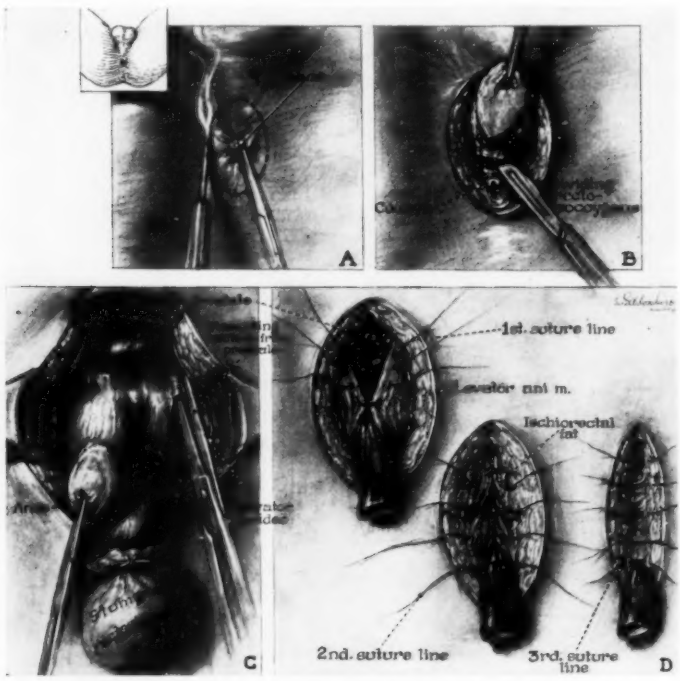


FIG. 7. Perineal Resection of Anus and Rectum

The patient has been placed in the dorsal lithotomy position.

a. Using the electrocautery an incision is made closely about the sutured anus.

b. The rectococcygeus muscle and fat are divided.

c. The levators are divided close to the rectum, the recto-sigmoid is delivered and the dissection between rectum and prostate completed.

d. The perineal wound is closed in layers about a tissue drain.

general condition had been improved by an ileostomy three years before, but discharge of blood and pus continued, and barium enema showed a hopelessly scarred and contracted colon.

Operation: December 11, 1947 (M. M. R.) Through a lower midline incision

under nitrous oxide-oxygen-ether anesthesia the Dragstedt ileostomy was disconnected, the terminal ileum, entire colon and rectum resected, and an anal ileostomy constructed. The patient received 1000 c.c. of citrated blood during the operative procedure which she withstood well. The specimen was a thickened, scarred colon, contracted and rigid as the result of severe chronic ulcerative colitis.

The patient was up walking on the fifth day. On the sixth day she passed stool and on the seventh day the indwelling intestinal tube was removed. All wounds healed per primam. She was discharged from the hospital January 10, 1948, one month after operation, with almost complete sphincter control.

In the first year following operation she had several bouts of prolonged diarrhoea associated with major emotional crises. She is now fully employed, vigorous and well and entirely continent of feces on an unrestricted diet and is trying to lose weight.

Summary: One stage total colectomy and anal ileostomy was performed in a 36 year old woman for ulcerative colitis of eleven years duration, and three years after establishment of an abdominal ileostomy. No complications attended the resection, and there is a good adjustment to the anal ileostomy.

#2 M. R. JHH #341806. This patient, a 26 year old soldier's wife, had had severe ulcerative colitis for seven years, with pain, bloody diarrhoea, edema of the legs and leg ulcers. An abdominal ileostomy had appeared to give relief, three years before, but attempted closure of the ileostomy failed. The ileostomy had to be restored and was thereafter poorly tolerated. The patient spent her nights face down on a canvas cot with a hole cut out for her constantly draining ileostomy. She was thin, moderately anemic (9.5 gms.) showed edema of the extremities and puffy eyelids although her serum albumin/globulin ratio was 4.5 gm.%/2.6 gm.%. Roentgenograms demonstrated extreme scarring of the colon with pseudopolyposis which was also seen through the sigmoidoscope.

Operation: February 14, 1948 (M. M. R.) Through a lower midline incision under nitrous oxide-oxygen-ether anesthesia, the ileostomy was disconnected, the terminal ileum, entire colon, and rectum resected and an anal ileostomy constructed. The patient received 2000 c.c. of citrated blood during the procedure which she withstood well. The specimen showed the typical scarring, induration, ulceration and polypoid regeneration of insular areas of mucosa, typical of long standing chronic ulcerative colitis (fig. 8).

She was up and walking on the third day. Five days after operation her anal ileostomy was discharging feces and the indwelling intestinal tube was removed. All wounds healed per primam. She was discharged from the hospital, March 4, 1948 nineteen days after operation with some degree of sphincter control but with troublesome diarrhoea.

Her subsequent course has been one of slow adjustment to diarrheal stools and for a long time peri anal excoriation was a severe problem. Ultimately her leg ulcers healed, edema of the legs and puffiness of the eyes disappeared, and with adjust-

ment of a troublesome social situation she assumed her full responsibilities. She has 3 to 5 stools in twenty-four hours and has sphincter control adequate except for the watery stools which she has occasionally and which demand prompt evacuation.

Summary: One stage total colectomy, resection of the rectum and anal ileostomy was performed for ulcerative colitis of seven years duration in a 26 year old woman

FIG. 8. Case #3 M. R. Specimen of terminal ileum, entire colon, recto-sigmoid, and cuff of rectal mucosa and submucosa from a patient with chronic ulcerative colitis. The bowel is rigid and thick-walled, with an edematous, contracted mesentery. There is scarring and destruction of the mucosa.

who had had her ileostomy for three years. No complications attended the resection. Adjustment to the anal ileostomy was slow, but ultimately satisfactory.

#3 I. G. JHH #451998. This patient, the 23 year old sister of a gastro-enterologist, had a fifteen year history of severe ulcerative colitis. She had had an ileos-

tomy at the age of 16, seven years before. Recurrent episodes of severe rectal bleeding were in contrast to a well maintained state of nutrition. She was admitted during a bout of bleeding.

Barium enema demonstrated a small, contracted, inflexible left colon with fuzzy irregularity of the mucosa of the right colon, interpreted as far advanced colitis on the left with early changes on the right.

Operation: March 5, 1948 (M. M. R.) Through a lower midline incision, under nitrous oxide-oxygen-ether anesthesia, the ileostomy was disconnected. The terminal ileum entire colon and rectum were resected and an anal ileostomy constructed. The patient received 2000 c.c. of citrated blood during the operation which she withstood well.

The specimen showed advanced changes of chronic ulcerative colitis in the left colon, sharply demarcated in the mid transverse colon from the right colon which was the seat of an intensely angry diffuse hemorrhagic colitis.

Her post operative course was outstandingly smooth. She was up and walking on the fourth day after operation. Four days after operation her anal ileostomy was discharging feces and her indwelling intestinal tube was removed. All wounds healed per primam. She left the hospital March 21, 1948, sixteen days after operation and on the last two days had been completely continent. Several months later a stricture of the anus had to be dilated under anesthesia.

She engages in ordinary activity, drives her own car, eats well on an unrestricted diet. Follow-up has been erratic, but she apparently remains continent and satisfactorily adjusted.

Summary: One stage total colectomy, resection of the rectum and anal ileostomy was performed in a 23 year old woman for ulcerative colitis of fifteen years duration, seven years after abdominal ileostomy. No complications attended the resection. Adjustment to the anal ileostomy was unusually rapid and continues satisfactory.

#4 E. A. JHH #470005. This patient, a 39 year old housewife, had been known for two years to have polypoid adenomatosis of the colon. Several of the polyps had grown so large as to require laparotomy and colotomy to relieve obstruction. Through the sigmoidoscope innumerable polyps were visible and barium enema indicated polypoid adenomatosis of the entire colon.

Operation: August 13, 1948, (M. M. R.) Through a lower midline incision under nitrous oxide-oxygen-ether anesthesia, the entire colon and rectum were resected and an anal ileostomy constructed. The patient received 2500 c.c. of citrated blood during the procedure which she withstood well. The specimen showed innumerable polyps covering the mucosa from the anal margin to the ileo caecal valve. None appeared carcinomatous.

She was up and walking on the fourth day after operation. Seven days after operation her anal ileostomy began to discharge feces and her indwelling intestinal tube was removed. All wounds healed per primam. She left the hospital September

10, 1948, twenty-eight days after operation having irregular control of her ten to twelve daily stools.

Since then she has gained heavily in weight so that that is her chief complaint. She is active and vigorous, has good sphincter control, but is still plagued by intermittent diarrhoea. Her peri anal skin has remained healthy.

Summary: One stage total colectomy resection of the rectum and anal ileostomy was performed for polypoid adenomatosis of the colon in a thirty-nine year old woman. No complications attended the procedure. Diarrhoea is still intermittently a serious problem.

#5 C. M. JHH #466987. This patient was a 41 year old pipe-line foreman who was accidentally discovered to have polyps in his colon. Sigmoidoscopy showed inummerable tiny polyps. Barium enema failed to show even these.

Operation: November 4, 1948 (Dr. H. W. Scott & M. M. R.) Through a lower midline incision under nitrous oxide-oxygen-ether anesthesia the entire colon and rectum were resected and an anal ileostomy was constructed. The patient received 2000 c.c. of citrated blood during the operation which he withstood well. The specimen showed the rectum and entire colon studded with small polyps.

Distention was a problem for a few days and the patient manifested a peroneal pressure palsy which delayed his recovery. The indwelling intestinal tube was removed on the fourth day. Wounds healed per primam. He left the hospital Dec. 10, 1949, thirty-six days after operation.

He returned April 11, 1949 for excision of residual ileal "hemorrhoids"—everted ileal mucosa. He had had a single involuntary stool in the interval since discharge and could go as long as eight hours without a bowel movement. He has not answered inquiries and has not been seen since.

Summary: Total colectomy, resection of the rectum and anal ileostomy were performed in one stage for polypoid adenomatosis of the colon in a 41 year old man. A peroneal palsy complicated his convalescence. A good result was apparently achieved with the anal ileostomy.

#6 J. R. JHH #501122. This patient was a forty-three year old housewife with a six year history of ulcerative colitis of progressively increasing severity. A fistula in ano had developed five months before. Barium enema showed a rigid contracted bowel and sigmoidoscopy showed extensive ulceration and scarring.

Operation: July 11, 1949, (Dr. E. S. Stafford) Through a transverse supra-umbilical incision under nitrous oxide-oxygen-ether anesthesia, the entire colon was resected, abdomino perineal resection of anus and rectum performed and an abdominal ileostomy constructed. The patient received 1500 c.c. of citrated blood during the procedure, which she withstood well. The specimen showed extreme changes characteristic of chronic ulcerative colitis. The indwelling intestinal tube was removed on the third day and the patient was up walking on the fourth day. Both wounds healed per primam. She left the hospital well on the nineteenth day. She has not answered communications since.

#7 D. S. JHH #505944. This patient was a twenty-nine year old woman who had severe ulcerative colitis for three and half years, with continued discharge of blood and pus, dermatitis, and arthritis after ileostomy. Barium enema showed a rigid, narrow, tubular colon, and sigmoidoscopy revealed an ulcerated scarred mucosa, dripping pus. Her emotional stability was so poor in the period after establishment of the abdominal ileostomy that it was decided not to perform an anal ileostomy, but an ordinary total colectomy and abdomino-perineal resection of the rectum and anus.

Operation: October 17, 1949 (J. C. H.) Through a lower midline incision, under nitrous oxide-oxygen-ether anesthesia, the entire colon, rectum and anus were resected. The patient received 2000 c.c. of blood during the procedure which she withstood well. The specimen showed the characteristic changes of severe chronic ulcerative colitis.

The patient was up and walking on the third day and the indwelling intestinal tube was removed on the same day. All wounds healed per primam and the patient left the hospital on the tenth day. She has continued well and gains weight steadily.

Summary: Total colectomy and abdomino-perineal resection were performed in one stage for ulcerative colitis of three and a half years duration in a woman of twenty-nine who was considered too unstable for an anal ileostomy. She has done well.

#8 L. A. JHH #319595. This was a thirty year old man with a six year history of ulcerative colitis for which an ileostomy had been performed in the first year of the disease. He had been well and comfortable for four years when pain and discharge of blood and pus per rectum recurred.

Barium enema showed a short, "lead pipe" colon and sigmoidoscopy revealed advanced disease. He was known to be erratic and undependable and total colectomy without anal ileostomy was elected.

Operation: November 7, 1949 (J. C. H.) Through a lower mid-line incision under nitrous oxide-oxygen-ether anesthesia, the entire colon, rectum, and anus were resected abdomino perineally. The patient received 1500 c.c. of citrated blood during the procedure which he tolerated well. The specimen showed the characteristic changes of severe chronic ulcerative colitis.

The indwelling intestinal tube was removed on the third day, and he was up and walking on that day. All wounds healed per primam and he was discharged two weeks after operation. He has had no difficulty since.

Summary: Total colectomy and abdomino perineal resection of the rectum in one stage were performed on a thirty year old man with ulcerative colitis of six years duration. No complications attended the resection. His mental attitude was incompatible with the cooperation required of a patient in whom an anal ileostomy is to be performed.

#9 N. S. JHH #529750. This patient was a 34 year old housewife, one of five children known to have polypoid adenomatosis of the colon. One sister had had

completion of colectomy and establishment of anal ileostomy, a year previously, in this hospital. A barium enema of the present patient taken in 1947 because of the family history, demonstrated the polyps. She had now had bloody diarrhoea for three months.

Polyps were palpable in the rectum and visible as far as the sigmoidoscope would reach.

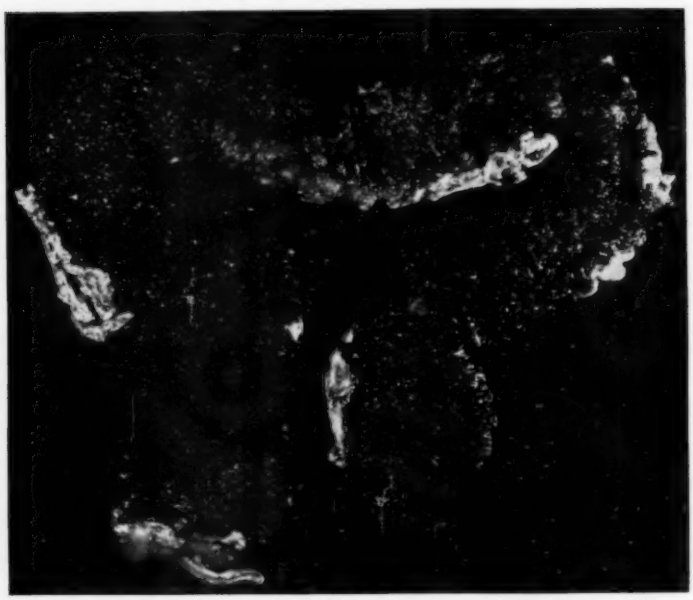


FIG. 9. Case #10 E. K. Specimen of terminal ileum, entire colon, and rectal muscosal and submucosal cuff from a patient with polypoid adenomatosis and hepatomegaly. The mucosa of the bowel is literally carpeted with myriad polyps which have completely replaced the normal tissue. No evidence of malignant degeneration was found.

Operation: March 4, 1950 (M. M. R.) Through a lower midline incision under nitrous oxide-oxygen-ether anesthesia a total colectomy, rectal resection and anal ileostomy was performed. The patient received 2000 c.c. of whole blood during the procedure which she withstood well. The specimen showed innumerable polyps from the anal margin to the ileo caecal valve.

The patient was up and walking on the fifth day. The anal ileostomy began to discharge on the fifth day and the indwelling tube was withdrawn the eighth day.

The wounds healed per primam and the patient was discharged April 10, 1950 on the thirty-seventh day with steadily improving control over the ileostomy. At the present writing she continues to improve.

Summary: Total colectomy, rectal resection and anal ileostomy were performed in one stage in a thirty-four year old woman with familial polypoid adenomatosis of the colon. No complications attended the resection. She appears to be acquiring satisfactory control.

#10 E. K. JHH #534088. This patient was a 31 year old woman admitted to the hospital with left lower quadrant pain, metrorrhagia and anemia. Polyps were palpable to the level of the anus on digital rectal examination. Barium enema demonstrated polyps over the entire colon. Hepatomegaly and splenomegaly of undetermined origin and a hemoglobin of 8 gms. complicated the picture and are not yet explained.

Operation: May 1, 1950 (Drs. Denton Cooley & M. M. R.) Through a lower midline incision, under nitrous oxide-oxygen-ether anesthesia, the entire colon and rectum were resected and an anal ileostomy constructed. The patient received 1500 c.c. of citrated blood during the procedure which she withstood well. The specimen (fig. 9) showed the most extraordinary carpeting of the bowel with polyps from caecum and appendix to anal canal.

She is still in the hospital. A pelvic hematoma developed and required evacuation. Her hepatic difficulties persist.

Summary: The entire colon and rectum were resected and an anal ileostomy constructed in one stage in a thirty-one year old woman with polypoid adenomatosis whose condition was complicated by unexplained splenomegaly and hepatomegaly. This is written only three weeks after the operation.

The procedure has been carried out in ten cases. Of this group four patients (#4, E. A.; #5, C. M.; #9, N. S.; #10, E. K.) had polypoid adenomatosis and the remaining six were afflicted with chronic ulcerative colitis. All but one of the patients in the latter group had functioning abdominal ileostomies for periods varying from three months to six years preceding colectomy. In seven of these ten cases anal ileostomy was carried out in conjunction with the procedure.*

Three of the patients with polyposis were in excellent physical con-

* Since this report was submitted #9 N. S. has developed complete sphincter control. However, the pelvic hematoma in #10 E. K. became infected and she left the hospital with an abdominal ileostomy. Two additional one stage total colectomies have been performed for ulcerative colitis. In one anal ileostomy failed because of infection and the patient left the hospital with an abdominal ileostomy. The last patient had a fecal fistula of the transverse colon and a history of perianal abscesses. A one stage total colectomy, abdomino perineal resection and abdominal ileostomy was successfully performed.

dition preoperatively. The fourth (#10, E. K.) was markedly anemic and had unexplained hepatomegaly and splenomegaly. On the other hand, the six patients suffering from chronic ulcerative colitis had had the series of remissions and exacerbations characteristic of this disease. In every instance, however, the patient's pre-operative condition, if not optimal, was at least stable and not in a fulminating stage, although one of these patients (I. G.) had had a serious hemorrhage one week preceding colectomy.

The benign post-operative course enjoyed by these patients has been gratifying and impressive. Aside from a temporary peroneal palsy which appeared in one patient (#5, C. M.) and the pelvic hematoma and hepatitis which have presented in another (#10, E. K.), there has been no event to mar the course of any case. All wounds healed per primam and without infection.

SUMMARY

A technique is presented for one-stage abdomino-perineal resection of the entire colon and rectum, using a lower mid-line abdominal incision.

Ten patients,* four with congenital polyposis of the colon, and six with chronic ulcerative colitis have undergone this procedure. There have been no deaths.

The technical feasibility of the operation and the satisfactory convalescence of these patients indicate the applicability of the operation in the treatment of patients requiring resection of the entire colon and rectum.

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* Two more patients have successfully undergone resection of the entire colon and rectum since this report was submitted.

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MODE OF ACTION OF HEAT LABILE SERUM INACTIVATING SUBSTANCE ON NEWCASTLE DISEASE VIRUS*

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The lethal or inactivating effect of various normal fresh sera on viruses (1, 2) bacteria (3, 4) and helminths (5) has been described but the effect itself remains largely unexplained. Interest in the virucidal characteristics of normal human and other mammalian sera has been recently stimulated by the finding that several undiluted normal sera will neutralize or inactivate large amounts of certain viruses including that of Newcastle disease of chickens (2, 6). The properties of such a heat labile serum factor or factors indicate that it may play a rôle in the resistance of a host to an invading virus.

In order to arrive at some understanding of this rôle, we have studied the occurrence and distribution of substances neutralizing Newcastle virus in various human and mammalian sera and tissue extracts. We have determined a number of variables influencing their activity in vitro, particularly the time of reaction and concentration of virus and serum.

Finally, we have measured the neutralizing substance in the sera of patients with several infectious diseases and have made similar measurements with the serum and tissues of several animals infected with Newcastle virus.

METHODS

Strain "B" (7) of Newcastle disease virus was used throughout these tests. In the great majority of tests serial dilutions of virus were combined with equal volumes of undiluted freshly obtained sera. This was usually obtained by allowing the blood to clot for one to three hours in a sterile petri dish. Tests for neutralization were routinely carried out after an hour's incubation of the mixture at 35°C. The procedure was to inoculate one drop of the mixture of serum and diluted virus

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on each of four or five chick embryos on the chorio-allantoic membrane. These embryos were followed for six days thereafter. Those dying on the first day from any cause are excluded from the 50 per cent end point calculation as are those found to have bacteria present. Tests were done essentially as in previous studies (8). The amount of virus neutralized is calculated by subtracting the logarithm of the LD_{50} of the virus serum combination from that of the control mixture. The control consisted of a similar dilution of virus with heated (56°, 30 min.) chicken sera and incubated similarly.

Hemagglutination and hemagglutination inhibition tests were followed by reading the patterns at the bottom of tubes after 45 minutes to 1 hour had elapsed. The tubes were kept at room temperature (20°–25°C) except during the hot summer

TABLE I

Heat Lability of Serum Factor Neutralising Newcastle Virus

	TITER OF VIRUS SERUM COMBINATION HEATED AT 56° C FOR:							
	Unheated	5 min.	10 min.	15 min.	20 min.	40–45 min.	80 min.	Control normal heated chicken sera
Human (M.F.)								
Exp. I								
LD_{50} of combination	2.5	4.5		3.7		4.6		7.5
LD_{50} neutralized	5.0	3.0		3.8		2.9		
Exp. II								
LD_{50} of combination	2.5*		5.5		5.5	3.9	5.5	
LD_{50} neutralized			2.0		2.0	3.6	2.0	
Rabbit								
Exp. III								
LD_{50} of combination	4.4		7.0		8.4	7.0		7.3
LD_{50} neutralized	2.9		0.3		−1.1	0.3		

* Combination of virus and serum in refrigerator for ½ hour before inoculation.

months when the sedimenting red cell-virus mixture was placed in a cooled box (16°C) during the time of development of the agglutination.

Interpretation: Our experience would indicate that differences of less than a logarithm (10 LD_{50}'s neutralized) should not be considered significant. Differences over one and a half logarithm are considered significantly different.

Degree of Lability: In a previous paper (8), the question of combined action of antibody and complement against the virus was examined. Freshly drawn sera were heated for varying periods of time and it was noted that the heat labile component was destroyed by as little as five minutes heating at 56°C.

Similar tests carried out with fresh rabbit serum show that it also is inactivated by relatively short periods of heating (Table I). We have not determined

the minimum heat or time necessary to destroy its activity. Freshly separated sera keeps a high degree of neutralizing activity during one or two days at 4°C.

RESULTS

Presence of neutralizing substance in sera and tissue extracts of various animals

One of the first questions raised following the demonstration of this serum activity was whether it plays an important or even moderately significant rôle in the resistance of those animals known to be insusceptible or only partially susceptible to the agent of Newcastle disease. Normal human plasma obtained by centrifuging blood in silicone tubes without any other treatment does inactivate the virus (8). Man may develop a conjunctivitis if presumably large inocula enter the conjunctival sac (9, 10), but there are no proven complications. Chickens which are the natural host have only minimal neutralizing activity in their sera. The neutralizing activity of the chicken sera and a few tissue extracts of several other animals are given in Table II. It will be noted that mice which will develop pneumonia following large intranasal inocula and may also develop an encephalitis when given the virulent strain intranasally do not have any demonstrable neutralizing substance in their sera or in extracts of the ground lungs, but may have slight neutralizing activity in some spleen extracts.

It would be preferable in a study such as this to work only with sera from one animal species, for there can be no proof at present of the assumption that a heat labile neutralizing factor present in human sera is identical or even closely similar to neutralizing substances in fresh rabbit sera. Our interest, however, in the reaction in the human host plus the greater activity of human sera has led us to perform many tests with these sera. The need for experimental inoculation of an animal and the determination of the effect of such inoculations on the neutralizing activity of animal sera has led to a series of experiments with rabbit sera. We will throughout this paper keep the data concerning the two types of sera completely separate.

Effect of time of combination

The original neutralization tests with human sera run by Howitt against Newcastle virus (11) were carried out with a mixture of un-

diluted sera and varying dilutions of virus incubated together for a half hour before embryos were inoculated. One of the first things then to determine was the effect of time. There was little or no immediate reaction between the heat labile serum factor and the virus, but progressive inactivation occurred over a two hour period. This was first

TABLE II

LD_{50} Neutralized by Sera or Tissue Extracts of Various Animals Serum and Virus Combined for 1 Hour at 35°C

ANIMAL	SERUM	TISSUE	
	Log virus neutralized by undiluted sera tested here	Log of virus neutralized by 10% suspension	
		Lung	Spleen
Man	(4.7, 4.7, 4.8, 3.8), 3.7, 4.2+, (4.2+, 5.6), (4.6, 4.3), 4.6, 4.2, 5.1		
Monkey	4.7+, 3.7+, (4.7, 4.7), (2.4)*		
Rabbit	2.2, 4.5, 2.9, 3.1, 3.3, (3.6)†	−0.3, (<0.8)†	3.0, (<1.8)†
Ferret	3.3‡		
Rat	2.5		
Mouse			
A.K.	0.0	−0.3	−1.6
dbal	+0.5	+0.5	−0.5
dba2	−0.5		
Swiss		0.0	−0.1
Chicken	1.2, 2.3, (1.7),§ (2.3) ‖		

* Difference between a one to two heated and unheated normal monkey serum. Time of combination not controlled.

† Inoculated intranasally with undiluted Newcastle disease virus three days previous.

‡ Difference between a one to three dilution of a heated and unheated serum of convalescent ferret.

§ One-half hour combination in incubator.

‖ Two hour combination in incubator.

The parentheses include repeated titrations done on the fresh serum from one individual taken at different times.

apparent in our tests on the possible rôle of complement in the neutralization test wherein a serum containing both heat labile and heat stable substances (8) was studied.

Although the tests presented in Table III are done with sera from the individual who has heat stable neutralizing substances also, the

almost complete lack of effect of such fresh sera when the combination was inoculated immediately on the embryo shows that the effectiveness of the heat labile factor is dependent upon time of combination. Essentially similar results are obtained with another human serum and with fresh rabbit sera (Table IV). These results contrast with the effect of chicken immune sera which the time of in vitro combination has no effect but are similar to the effect of immune sera from rabbits and possibly man (8).

TABLE III

The Effect of Time of Combination of Serum with Virus Upon the Neutralization Titer of Unheated Human Serum (F)

	EXPERIMENT #1				EXPERIMENT #2	
Dilution of virus used	5–10 min.	½ hr. 4°C	1 hr. 35°C	Control, no incubation	5–10 min.	1 hr. 35°C
10^{-3}						
10^{-4}				2/3		
10^{-5}						
10^{-6}					0/4	
10^{-7}	2/4	0/3	0/4		0/5	
10^{-8}	3/4	1/2	0/4		1/5	0/5
10^{-9}	4/4	3/4	0/4		4/5	2/5
10^{-10}	3/3	4/4	0/3			0/5
10^{-11}						0/5
LD_{50} of combination	4.8	3.6	<1.5		3.5	<.5
LD_{50} neutralized	3.2	4.4	6.5+		4.2	7.2+

Effect of temperature

If there is an effect of time it might be expected that the temperature of the combining mixture would also have an effect. Using fresh rabbit and human sera we did obtain different degrees of virus inactivation at different temperatures. This, however, was not marked and neutralization was less at 16°C than at either 4°C or 35°C (Table V).

Effect of concentration of virus on amount neutralized

The nature of the neutralizing action of fresh serum on Newcastle virus is of course unknown. It becomes then of interest to define the reaction in terms of concentration of virus and serum factor. As indi-

TABLE IV

Summary of the Data on the Effect of Time of Combination of Virus and Fresh Serum on Neutralizing Activity of the Serum

						CONTROL		
		Immediate inoculation	½ hr. 35°C	1 hr. 35°C	2 hrs. 35°C	Immediate inoculation	1 hr. 35°C	2 hrs. 35°C
Fresh human sera with heat stable substances	LD_{50} of combination	4.8		1.5			8.3	
	LD_{50} neutralized	3.5		6.8				
Without heat stable substances	LD_{50} of combination	6.4	3.8	3.0				
	LD_{50} neutralized	1.9	4.5	5.3				
Fresh rabbit sera	LD_{50} of combination	6.0		4.2	4.2			7.3
	LD_{50} neutralized	1.3		3.1	3.1			
Fresh ferret sera*	LD_{50} of combination	5.0		1.0		7.0	7.2	
	LD_{50} neutralized	2.2		6.2				

* This serum was taken from a ferret following intranasal inoculation with Newcastle virus. When the serum was heated and tested for antibodies by 1 hour, 35°C incubation test there was neutralization of only one logarithm dose.

TABLE V

Effect of Temperature of Combination of Virus and Serum on Amount of Virus Neutralized by Fresh Sera

		4°C	16°C	35°C	HEATED CHICKEN CONTROL SERA 35°C
Experiment 1					
Rabbit Sera for 1 hour	LD_{50} of combination	4.4	5.0	3.2	7.7
	LD_{50} neutralized	3.3	2.7	4.5	—
Experiment 2					
Human (F.I.)	LD_{50} of combination	4.8	5.3	3.8	8.3
Normal Sera for ½ hour	LD_{50} neutralized	3.5	3.0	4.5	
Experiment 3					
Human Sera (M. F.) for 1 hour	LD_{50} of combination	4.0		2.7	7.0
	LD_{50} neutralized	3.0		4.3	

All tests were carried out in tubes and racks which had been kept at the indicated temperature for ½ hour before adding dilutions of virus. They were returned to incubator or controlled temperature immediately after combining at room temperature.

cated under METHODS in the majority of our tests we have determined the effect of undiluted sera on varying dilutions of virus. Following the incubation of the mixture of serum and virus for an hour, the combi-

nation is tested for its ability to produce infection. Such tests tell us the total amount of virus which can be completely inactivated. If however, a combination of serum and concentrated virus which is not completely inactivated is titered by dilution in saline (Table VI) or is centrifuged so that the serum inhibitors are greatly diluted, and the activity of the virus pellet is measured, we find that a large percentage of the original virus activity is lost. This usually amounts to between four and five logs of virus activity or an inactivation of some 99.99 per cent of activity.

If varying concentrations of virus are exposed to the undiluted serum it is found that with increasing concentration of virus, an increasing total amount of virus is activated but the actual percentage of virus

TABLE VI*

A Comparison of the Amount of Virus Inactivated by (1) Exposing Concentrated Virus to Fresh Serum and then Titering Residual Dilutions of Virus with (2) Exposing Different Dilutions of Virus to Undiluted Serum and then Titering

AMOUNT OF VIRUS	(1) Undiluted serum + undiluted virus			(2) Undiluted serum + dilutions of virus		
	Titer of control	Titer of exposed virus	Drop in activity	Titer of control	Titer of combination	Drop in activity
10× conc.	8.7	5.3	3.4	8.8	2.0	6.8
Undiluted allantoic fluid	8.3	2.7	5.6	9.0	1.7	7.3

* Tests in both Table VI and VII were carried out at 35°C incubation for two hours to allow completion.

inactivated tends to drop (Tables VI and VII). This may be compared with the effect of chicken immune serum (Table VIII).

Dilution of serum in relation to concentration of virus

In studies on the neutralization of virus by anti-sera considerable attention has been paid to the slope of the curve relating virus concentration to serum concentration (12, 14). It has been found that for different systems this slope has considerable variation. Using fresh serum of M. F. who also has heat stable neutralizing substances in her sera, we found the slope to be about 3.5; serum from F. I. who lacks such presumed antibodies but like all other human sera tested has a great deal of heat labile neutralizing activity an almost identical slope relationship obtained (Fig. 1). Instability of the neutralizing factor to

dilution was apparently ruled out by comparing the efficacy of fresh serum diluted in saline and in heated normal chicken sera (Table IX).

Unfortunately, all such relationships of virus and serum concentration reactions are based on the assumption that the reaction between the serum and virus has reached completion at the time of testing. The very fact that the reaction between fresh serum and virus

TABLE VII

The Effect of Fresh Undiluted Human Serum on Varying Concentrations of Washed Virus

CONCENTRATION OF VIRUS	CALCULATED NUMBER VIRUS PARTICLES	PARTICLES ACTIVE AFTER EXPOSURE	DROP IN LOG ACTIVITY
10×	$10^{9.0}$*	$10^{6.5+}$	<2.5
Undiluted	$10^{8.0}$	$10^{3.7}$	4.3
10^{-1}	$10^{7.0}$	$10^{2.4}$	4.6
10^{-2}	$10^{6.0}$	$10^{0.3}$	5.7

* Based on actual LD_{50} of the concentrate. The other figures in this column are calculated therefrom.

TABLE VIII

The Effect of Varying Concentrations of Washed Virus on the Degree of Virus Inactivation Produced by Immune Chicken Serum

CONCENTRATION OF VIRUS	CALCULATED NUMBER VIRUS PARTICLES	PARTICLES ACTIVE AFTER EXPOSURE	DROP IN LOG ACTIVITY
10×	$10^{9.0}$	6.3	2.7
Undiluted	$10^{8.0}$	5.0	3.0
10^{-1}	$10^{7.0}$	>3.5	>3.5
10^{-2}	$10^{6.0}$	1.7	4.3

in our system does take time in vitro may indicate that the reaction between virus and dilution of serum is not complete at 1 hour. In other words, if the rate of reaction between virus and serum were dependent upon serum concentration there would be a much greater difference between the amount neutralized by two dilutions of sera early in the reaction, than at the end. Actual tests of the rate of reaction between dilutions of serum and the virus (Fig. 2) indicated that such may be the case with certain sera.

Effect of serum factor on the virus

It is possible to measure the individual characteristics of the virus of Newcastle disease in a variety of ways. Among these are its capacity

to agglutinate red cells, its morphology, and its change in morphology when subjected to hypertonic salt concentrations (15, 16).

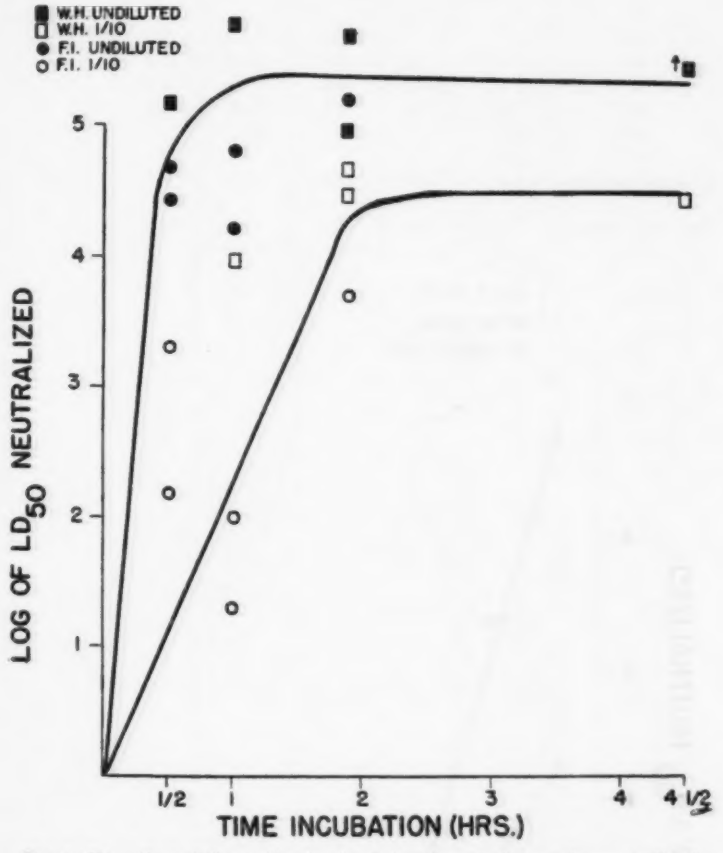

FIG. 1. The effect of time of incubation before inoculation on the neutralization titer of undiluted and 10% serum.

In most of the mammalian sera which we have tested the degree of inhibition of hemagglutination produced by unheated sera has not been greatly lowered by heating the sera (Table X and XI). This does not mean that the heat labile component has no effect on the capacity of

TABLE IX

The Effect of Dilution in Saline and Serum of the Heat Labile Neutralizing Fraction of Human Serum (F. I.)

DILUTION OF VIRUS USED	UNDILUTED	DILUTION OF HUMAN SERUM IN:				CONTROL UNDILUTED NORMAL CHICKEN HEATED SERUM
		1/10 in Saline	1/100 in Saline	1/10 in Undiluted Normal Sera	1/100 in Heated Chicken Sera	
10^{-9}						0/3
10^{-8}			2/4		3/4	3/4
10^{-7}		2/3	4/4	2/4	4/4	4/4
10^{-6}	0/4	3/4	4/4	4/4	4/4	
10^{-5}	0/4	4/4	4/4	4/4	4/4	
10^{-4}	0/4	4/4		4/4		
10^{-3}	4/4					
LD_{50} of combination	3.5	7.0	8.0	7.0	8.3	8.3
LD_{50} neutralized	4.8	1.3	0.3	1.3	0.0	

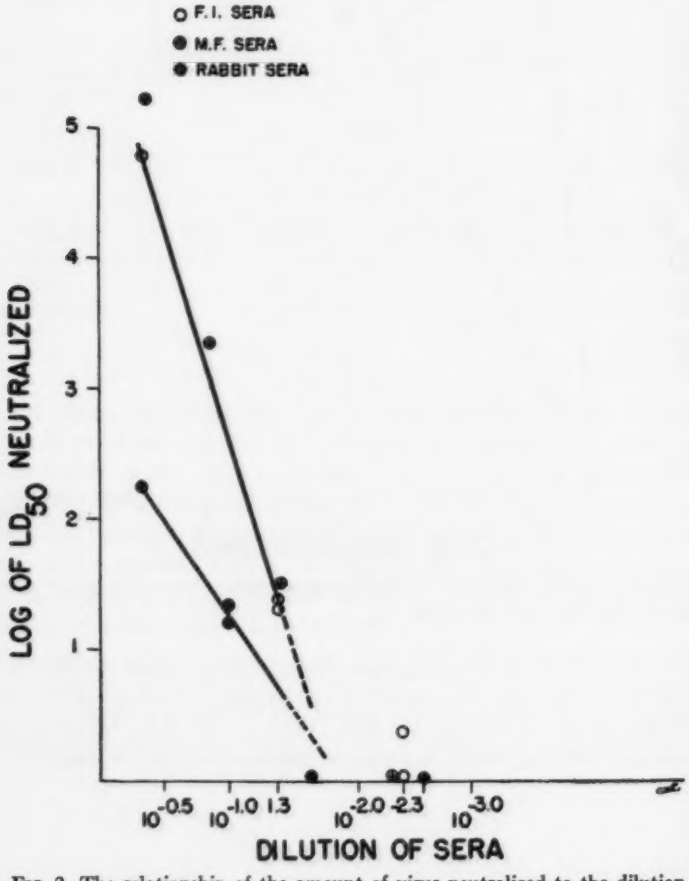

FIG. 2. The relationship of the amount of virus neutralized to the dilution of serum used in the test.

TABLE X

The Effect of Unheated and Heated (25 min. at 56°C) Human Sera on Hemagglutination by Freshly Harvested Newcastle (B) Virus

DILUTION OF SERUM	UNHEATED SERUM										HEATED SERUM									
	Dilution of virus										Dilution of virus									
	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2056	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2056
0	0	0									++	+								
1/2	0	0	0								+	+	+	+	++					
1/4			0	0	0	0	0	0	0	0			0	0	0	+	++	0	0	0
1/8			+	0	0	0	0	0	0	0				0	0	+	++	++	0	
1/16			0	0	0	0	0	0	0	0				++	++	++	++	+	0	
1/32			0	0	0	++	+++	+++	++	0					0	+	++	+++	++	0
1/64			+++	+++	+++	+++	+++	+++	+++	++					+++	+++	+++	+++	+++	+
1/128			+++	+++	+++	+++	+++	+++	+++	++										
Control, no serum											+++	+++	+++	+++	+++	+++	+++	+++	0	0

The fresh normal human serum tested 2–3 hours after venepuncture. Serum divided in two portions. One-half placed in 56°C water bath for 30 minutes. The other at 4°C. Virus centrifuged and concentrated 10× eight days previously and titering by red cell agglutination to 2,056. Serial dilutions of serum combined with virus at 35°C for 1 hour. Red cells added in cold saline. Then test placed at 16°C for 45 minutes before red cell pattern formation read.

the virus to agglutinate red cells. When either washed Newcastle disease virus or influenza A virus was placed in fresh sera and in heated sera for one hour at 35°C then centrifuged out of the serum and tested for the capacity to hemagglutinate, it was found that virus exposed to fresh serum was no longer capable of agglutinating red cells, whereas, that which had been similarly exposed to heated sera did still agglutinate chicken red cells.

Direct electron microscope observation of the virus after exposure to fresh serum failed to show any change in appearance of the virus. It is possible however to show that virus which is inactivated in a variety of ways loses some property, possibly osmotic of adjusting to

TABLE XI

The Effect of Unheated and Heated (25 min. at 56°C) Rabbit Sera on Hemagglutination by Freshly Harvested Newcastle (B) Virus

DILUTION OF SERUM	UNHEATED SERUM						HEATED SERUM					
	Dilution of virus						Dilution of virus					
	1/20	1/40	1/80	1/160	1/320	1/640	1/20	1/40	1/80	1/160	1/320	1/640
1/3	0						0					
1/6	0	0					0	0				
1/15	0	0	0	0	0	0	0	0	0	0	0	0
1/30	0	0	0	0	0	0	0	0	0	0	0	0
1/90	0	+++	+++	+++	+++	0	+++	+++	+++	+++	+++	0
0	+++	+++	+++	+++	+++	0	+++	+++	+++	+++	+++	++

Virus and serum together 20 min. at 16°C before red cells added. Tests at 16°C.

variations of salt concentration (15, 17). When virus which had been exposed as described above to (A) fresh, and (B) heated (control) sera was subsequently placed in the hypertonic saline it was found that the virus originally exposed to the fresh serum no longer changed shape in hypertonic saline in contrast to virus exposed to heated serum.

Effect of virus on serum

In the reaction between serum and virus it has been of interest to determine to some extent the potency of the serum factor. This was done by exposing virus to serum for one half hour at 35°C, then by centrifuging in a motor-driven centrifuge (17a) at about 15,000 r.p.m.

TABLE XII

Absorption or Destruction of Serum Factor by Virus Preparations

EXPERIMENTAL PROCEDURE	TITER OF ABSORBED SERUM + UNTREATED VIRUS	UNABSORBED SERUM + UNTREATED VIRUS (NDV)	NORMAL HEATED SERUM + VIRUS	VIRUS NEUTRALIZED BY ABSORBED SERUM	VIRUS NEUTRALIZED BY UNABSORBED SERUM
Fresh serum treated with 10× concentrated virus previously irradiated for 15 min. Serum and irradiated virus incubated at 35°C for 30 min. before separation by centrifugation.	6.0	3.5*	7.8	1.8	4.3
Fresh serum treated with 10× concentrated virus previously irradiated for 15 min. Serum and irradiated virus incubated at 35°C for 30 min. before separation by centrifugation.	6.4	2.6		1.4	5.2
Fresh serum treated with 10× concentrated virus previously irradiated for 15 min. Serum and irradiated virus incubated at 35°C for 30 min. before separation by centrifugation. Serum tested with concentrated virus.	4.7	2.2	8.2	3.5	6.0
Dilution 1/5 of virus concentrate	1.8			6.4	
Influenza virus used to absorb serum. This washed and concentrated 2× from original allantoic fluid.	4.5	2.8	7.0	2.5	4.2

for 50 minutes sedimenting most of the virus free from the serum. The supernatant of this serum which had thus been reacting with the virus, was then tested for its virus neutralizing activity. This was difficult because the amount of undiluted fresh virus, sufficient to produce a reduction in the neutralizing activity of the serum, is so large that active virus is left in the supernatant after centrifugation, thus invalidating the test. If, however, virus which has been inactivated by ultraviolet light is substituted in the preliminary part of the test, the supernatant from such a centrifugation contains little or no demonstrable infectiousness and any residual inactive virus is insufficient to "interfere" with active virus (18). Such serum has, however, lost increasing amounts of neutralizing activity as the concentration of virus increased (Table XII). All such tests were accompanied by a dilution of the serum in a volume of saline equal to the volume of virus suspension. This diluted serum was centrifuged simultaneously with the serum-virus mixture and the top layer of this serum saline mixture was used as one of the controls. One may conclude that only with large amounts (in the order of $10^{10.5}$ particles) of virus is it possible to either absorb or inactivate the serum component.

DISCUSSION

Our interest in the heat labile neutralizing factor is by no means limited to Newcastle disease virus, but extends to the general mechanism of the problem. We continue however to study this particular model because it is a convenient one.

Consideration of the action and importance of the serum factor which neutralizes Newcastle virus may conveniently be divided into several phases for purposes of discussion.

Distribution among serum fractions and species

There is a great need for a series of careful fractionations of serum with a determination of the exact fraction containing the serum neutralizing factor. In this connection one is reminded of the lipoprotein isolated by Utz (19, 20) from a variety of sera, which he has demonstrated to be active in neutralizing several viruses, including that of Newcastle. This factor is increasingly active with time and is found in several mammalian sera and in chicken sera. We have briefly determined the effect of ether extraction on the neutralizing activity

of fresh human serum and found a drop from 4.7 log virus neutralized to 3.0 log virus neutralized after such extraction. A series of precipitations of fresh human serum showed that the neutralizing activity was present in the globulin fraction obtained by Na_2SO_4 fractionation, and by $(NH4)_2SO_4$ fractionation and not in the albumin fraction.[1]

Kinetics of the Serum-Virus Reaction

The mode of action of the serum factor upon the virus is not clear. It appears that during the inactivation of the virus which proceeds in vitro, there is utilization of the serum factor, and that there is a relationship between dilution and rate of reaction. This is of particular interest since Burnet has also shown (21) that the rate of inactivation of bacteriophage by antiserum is dependent to a great extent upon the concentration of the antiserum. Presumably the heat labile component in serum has little to do with antibody as such, but the techniques of analysis of the reaction of the heat labile factor and of antibodies against viruses have been the same. This has been particularly true in discussions concerning the slope of the line expressing the relationship between the concentration of a serum and the amount of virus neutralized (12, 14). Our preliminary experiments indicated for us that such peculiar steep slope relationships also existed for the neutralization of Newcastle virus by the heat labile factor. Such slope relationships are valid, however, only if the reaction between serum and virus has reached completion in all dilutions. Whether detailed study of the antibody-virus systems when tested in the embryo would show a change in slope with an increase of time of incubation is not clear at this time, but it is worth pointing out that Burnet (12) found a slope relationship "nearer to 1 when the reagents were used at higher concentration," and that Walker and Horsfall (14) found that "The slope of the *in ovo* neutralization line obtained with mixtures held 24 hours at 4°C was of the order of 3." The slope is contrasted to one of 4.7 obtained when the virus-antibody combination is kept at 4°C for only a half hour before inoculation of the embryo.

Physiological importance

It is difficult to ignore a factor which when present in either serum or plasma is capable of inactivating many lethal doses of virus in a

[1] Courtesy of Dr. O. D. Ratnoff.

short time when reacting at body temperature. There are several ways however in which the possible physiological significance of this factor may be tested. We have begun to test for the presence of this factor in the sera of individuals with differing types of illness. These results are far from complete but do show the uniform presence of the substance at different ages and under different conditions. Sera from two cases of mumps were studied by us particularly because a change in neutralization titers of such patients has been reported (22). We found no lowering of the titer during the acute phase of the disease. No lowering of the titer of the neutralizing substance was detected in the serum

TABLE XIII

Neutralization Titer of Serum from Rabbit Inoculated Intravenously with Newcastle Virus

(Inoculated intravenously with stock frozen virus. Bled from opposite ear)

TIME AFTER INOCULATION		UNHEATED RABBIT SERUM	HEATED RABBIT SERUM	CONTROL (CHICKEN)
1 hr.	LD_{50} of combination	4.8		8.2
	LD_{50} neutralized	3.4		
24 hrs.	LD_{50} of combination	4.8		7.8
	LD_{50} neutralized	3.0		
4 days	LD_{50} of combination	3.0	5.8	7.2
	LD_{50} neutralized	4.2	1.4	
14 days	LD_{50} of combination	3.2	4.8	7.7
	LD_{50} neutralized	4.5	2.9	

of a rabbit given the Newcastle virus (undiluted allantoic fluid) intranasally three days previously (Table XIII) or in another rabbit given a similar inoculation intravenously. However, our experiments on the kinetics of the reaction would indicate that these dosages were inadequate.

The presence of a definite, but minimal neutralizing activity in fresh chicken serum (a susceptible animal) and the absence of such activity in mouse serum (an animal relatively resistant to the virus) is a clear demonstration that a variety of factors determine resistance and susceptibility but does not negate the possibility of the importance of this substance in vivo.

SUMMARY

A heat labile virus neutralizing factor is present in the sera of man, monkeys, rats, rabbits and in small amounts in chicken sera. It has not been detected in mouse sera. This factor does not react with the virus immediately but dependent upon concentration and possibly upon temperature attains a certain degree of virus inactivation within one to two hours. The reaction does not proceed appreciably beyond this point at the dilutions tested. Fresh human normal sera cause the virus to lose the capacity to agglutinate red cells and to change shape when placed in hypertonic saline.

With increasing amounts of virus exposed to the serum there is an increase in the total amount of virus inactivated but a decrease in the percentage of virus inactivated.

The high degree of activity of this substance in fresh sera and plasma and its uniform presence in such sera under a variety of conditions encourages the belief that it has significance in relation to resistance to disease.

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MARKED LIPEMIA RESULTING FROM THE ADMINISTRATION OF CORTISONE

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In a previous study from this laboratory (1), in which the effect of cortisone in inhibiting the cardiovascular lesions of hypersensitivity was described, it was found that the turbidity of the sera of the cortisone-treated animals interfered with the performance of the precipitin tests. Fat stains showed that the turbidity was due to the presence of fat droplets, and the fat had to be removed by extraction in order to perform the precipitin tests satisfactorily. Since in that study there was the complicating factor that all of the animals that received cortisone were also subjected to the serum sickness type of anaphylactic reaction by the procedure shown by Rich and Gregory (15) to favor the development of cardiovascular lesions of hypersensitivity,[1] it was desirable to learn whether cortisone would produce a comparable degree of lipemia in the normal animal, uncomplicated by serum sickness.

There is a virtual absence of pointed studies of the effect of pituitary adrenocorticotropic hormone (ACTH) or cortisone upon blood fats. Prior to the purification of ACTH, some investigators, using crude pituitary extracts, noted a rise in blood fats, while numerous others reported a fall (8). In studies in this laboratory, the daily administration of 10 to 20 mgm. of ACTH in divided doses did not increase the blood lipides of rabbits enough to produce a turbidity sufficient to interfere with precipitin tests (9, 11). Chemical analysis of the serum lipides in those animals was not carried out. Conn (2) has reported that ACTH produces a marked fall in serum cholesterol in the human being. Adlersberg, Schaefer and Dritch (13), on the contrary, report a

[1] Since the completion of these studies, Kobernick and More (Proc. Soc. Exp. Biol. and Med., 1950, **74:** 602) have reported the occurrence of lipemia in two rabbits sensitized by the same procedure, kept in the cold, and treated with cortisone.

rise. Regarding cortisone, Sprague and his coworkers (3), in their report on the metabolic effects of cortisone in the human being state: "The total (serum) cholesterol increased during the administration of cortisone in four cases out of six in which determinations were made, but the data are not adequate to establish the validity of the observation." Adlersberg and his coworkers (13), likewise, report that cortisone causes a rise in serum cholesterol in man. Conn (2), on the other hand, was unable to demonstrate any significant change in serum cholesterol in human beings treated with 200 mgm. of cortisone per day. Thorn (5) found no change in serum cholesterol in patients who had normal levels at the beginning of treatment with 100 mgm. of cortisone per day. Kendall (4) states that five days after beginning treatment with cortisone in a patient with nephrosis a rise occurred in both the cholesterol and total fats of the serum. Thorn (5), on the contrary, found a fall in serum cholesterol in a nephrotic patient treated with cortisone. It may be that some of these contradictory reports are due to differences in dosage and in the duration of treatment.

The experiment upon which the present report is based comprised a series of 57 male albino rabbits averaging about 2200 grams in weight. The animals were kept in separate cages in the same room, and were given an unrestricted amount of Purina Rabbit Chow Checkers and water. Six of the animals (Group I) were given a single daily intramuscular injection of 7.5 mgm. of cortisone (Lot 404 of Merck's Cortone[2]) for 16 days, with no other treatment. Fifteen animals (Group II) were given a single intracorneal injection of about $\frac{1}{10}$ cc. of sterile horse serum (without preservative).[3] This treatment induces the development of hypersensitivity, but does not produce serum sickness. This group received the same dosage of cortisone as the animals of Group I, and for the same period of time. Eighteen animals (Group III) were given a single intravenous injection of sterile horse serum without preservative—a treatment that favors the development of serum sickness (15). These animals also received horse serum intracorneally and cortisone intramuscularly just as in Group II. Eighteen animals (Group IV) received intravenous and intracorneal horse serum as in Group III, but were given no cortisone. The daily dosage of

[2] The cost of the cortisone was defrayed by the U. S. Public Health Service.

[3] The horse serum was generously supplied by Sharp and Dohme, Inc.

cortisone in each treated animal was equivalent, by kilogram of body weight, to between 150 and 225 mgm. for a human being weighing 132 lbs. As stated above, this dose was given for a period of 16 days.

On the day following the last injection of cortisone blood was withdrawn, without anesthesia, by cardiac puncture from all of the animals.

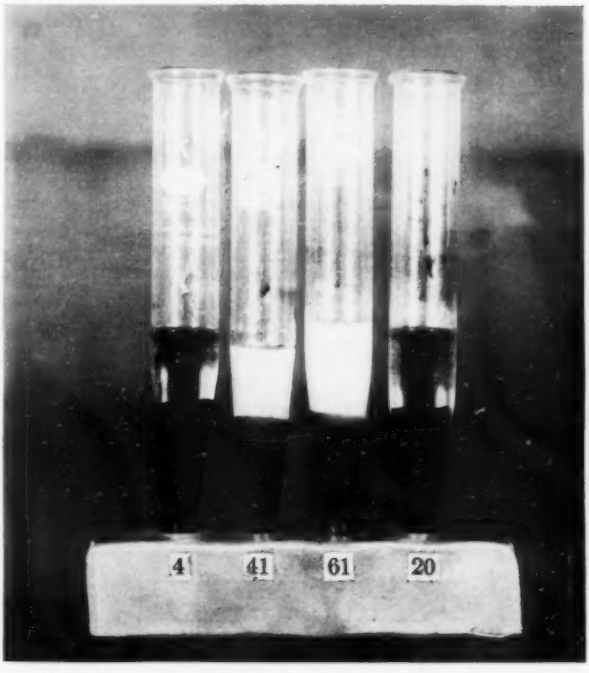

FIG. 1. Note the opaque, milky appearance of the sera of cortisone-treated rabbits 41 and 61, in comparison with the normally clear, transparent sera of rabbits 4 and 20 which received no cortisone. (Photograph by Miss Joan Wheaton)

It was evident from visual inspection of the centrifugalized blood that the sera of all of the 18 animals that did not receive cortisone (Group IV) were clear and transparent, whereas the sera of 33 of the 39 animals that received cortisone (Groups I, II and III) were grossly turbid or milky (Fig. 1), and fat stains showed the presence of fat droplets. Table

TABLE I

Lipemia in Cortisone-Treated Animals, and Weight Change in Grams and in Percentage of Body Weight

GROUP IV INTRAVENOUSLY SENSITIZED, NO CORTISONE			GROUP III INTRAVENOUSLY SENSITIZED, CORTISONE-TREATED			GROUP II INTRACORNEALLY SENSITIZED, CORTISONE-TREATED			GROUP I NORMAL, NON-SENSITIZED, CORTISONE-TREATED		
Rabbit	Lipemia	Weight Change	Rabbit	Lipemia	Weight Change	Rabbit	Lipemia	Weight Change	Rabbit	Lipemia	Weight Change
		gms.			*gms.*			*gms.*			*gms.*
1	0	+400 (20%)	7	+	+85 (3.9%)	11	++	−75 (3%)	70	+++	−125 (7.6%)
2	0	+475 (26%)	9	0	−125 (5.5%)	12	++	−100 (4%)	71	+	−200 (9.2%)
4	0	+225 (11.2%)	10	++	−175 (7.5%)	13	0	−200 (8.8%)	73	+	−325 (13.7%)
5	0	+250 (12.3%)	21	++	−75 (3.6%)	15	++	−100 (4.3%)	74	++	−100 (4.2%)
16	0	+350 (15.5%)	23	++	+25 (1%)	27	+	−200 (10.6%)	75	++	−150 (6.5%)
17	0	+400 (19.5%)	25	0	−350 (16%)	28	+	−225 (11.2%)	76	+++	−350 (16%)
18	0	+400 (22.5%)	36	++	0	29	++	+50 (2.5%)			
19	0	+150 (7.4%)	37	++	+100 (5.6%)	41	++	0			
20	0	+250 (12.8%)	38	+	−400 (18%)	42	++	+150 (7.7%)			
31	0	+25 (0.8%)	39	++	+175 (7.6%)	43	++	−200 (10.8%)			
32	0	+325 (15.6%)	40	++	−650 (29%)	44	++	−225 (7.8%)			
34	0	+275 (13.7%)	52	+++	−250 (10.5%)	57	0	−150 (7.3%)			
47	0	+150 (5.2%)	53	+++	−200 (9.3%)	59	0	−100 (4.8%)			
48	0	+225 (9.9%)	54	+	+150 (6.6%)	60	+	−225 (10.8%)			
49	0	+400 (18%)	55	++	−350 (17.5%)	63	++	−100 (4.7%)			
50	0	+700 (35%)	56	++	+75 (4%)						
58	0	+775 (42.4%)	61	+++	−175 (7.9%)						
68	0	+375 (18.7%)	62	0	−400 (25%)						

I shows the relative degree of lipemic turbidity in the various groups. The degree of turbidity was estimated visually. As a check, Dr. Norman Weissman kindly made an independent grading of the relative turbidity of the sera of all of the animals of one of the cortisone-treated groups, using a Coleman Model 14 spectrophotometer. His readings were completely in accord with our visual estimation. No attempt is made to list all degrees of turbidity in Table I. In that table, one plus signifies definite but not marked turbidity; two plus, marked turbidity; three plus extreme turbidity. Table II presents chemical analyses of

TABLE II

	SERUM TOTAL FATTY ACIDS, MGM. PER 100 CC.*	SERUM TOTAL CHOLESTEROL MGM. PER 100 CC	SERUM PROTEINS, GMS. PER 100 CC
Normal, no cortisone, #77	202.2	65	Alb. 3.9 Glob. 1.8
Normal, no cortisone, #78	202.2	52	Alb. 4.1 Glob. 2.4
Sensitized, no cortisone (pooled nos. 1, 4, 16)	108.		
Sensitized, no cortisone, #20		45	
Unsensitized, cortisone, #75	692.5	102	Alb. 4.1 Glob. 1.4
Unsensitized, cortisone, #76	897.5	112	Alb. 4.6 Glob. 1.4
Sensitized, cortisone, (pooled nos. 12, 21, 40, 42, 53)	914.0		
Sensitized, cortisone #41		90	
Sensitized, cortisone #61		85	

* Method of Stoddard and Drury, Jour. Biol. Chem., 1929, *84*, 741.

the sera of representative animals of each experimental group, and of two normal male albino rabbits which were of approximately the same weight as the experimental animals, and were kept on the same diet under the same environmental conditions.[4] It is clear that cortisone produces a marked degree of lipemia in rabbits, and that both the total fatty acids and cholesterol participate in the lipemia. It will be noted that the lipemia was not accompanied by a lowering of the plasma proteins.

[4] We are indebted to Mrs. Florence B. White, Director of the Clinical Chemical Laboratory of the Department of Medicine, for making these analyses.

It has been recognized for some time that the adrenal cortex exerts an effect upon fat metabolism, though the precise nature of the effect and the mechanism by which it is produced are by no means clear at present. That cortical hormone increases the utilization of fat is indicated by the fact that adrenalectomized animals exhibit a decreased response to ketogenic agents and conditions, while both ACTH and cortisone enhance ketosis. Baker and his coworkers (7) demonstrated that purified ACTH causes a deposition of fat in the liver, an action suggested by the studies of previous investigators who had used less purified extracts of the anterior lobe of the pituitary. The action of ACTH in causing a deposition of fat in the liver has been confirmed in this laboratory. As regards cortisone, Selye (6) states: "We have not seen fatty livers after cortisone." In the present study the livers of most of the cortisone-treated animals contained marked deposits of fat in droplets of very large or smaller size, and this was the case in the cortisone-treated animals of a previous study from this laboratory (1). There can be no doubt that, in the rabbit at least, cortisone causes the deposition of fat droplets in the liver to a striking degree.

The precise manner in which cortisone acts to produce lipemia is not clear at present. Lipemia may result from an increased absorption of fat from the intestinal tract; from an increased mobilization of fat from the fat depots into the blood in conditions demanding an increased utilization of fat; or from as yet not understood conditions (*e.g.*, in nephrosis). While there are studies suggesting that adrenal cortical hormone may promote the absorption of fat from the intestines (10), it is unlikely that the lipemia in the cortisone-treated animals of the present experiment was due principally, if indeed at all, to increased fat absorption. In the first place, both Bloor (16) and Horiuchi (14) have found that rabbits, when placed on a high fat diet, do not develop alimentary lipemia as readily as carnivorous or omnivorous animals. The diet of the animals in the present experiment contained only 2.25% of fat. In the second place, the food cups were removed from the cages early in the morning on the day that the blood was withdrawn, and there were no differences between the degree of visible lipemia in the first sera obtained after removal of the food from the cages and that in the sera obtained at intervals throughout the day until late afternoon when the last bloods were withdrawn.

It is known that the C-11-oxygenated cortical steroids, of which cortisone is a member, promote gluconeogenesis, and there is also evidence that they inhibit the utilization of carbohydrate (17); and the increased ketosis produced by these steroids is evidence of increased utilization of fat. The lipemia in our cortisone-treated animals may therefore represent an increased fat transport from the fat depots, conditioned by depressed carbohydrate utilization and increased fat utilization. It may be stated, however, that there was no absolute parallelism between the degree of lipemia and the degree of glycosuria. It will be recalled that in diabetes mellitus, also, in which there is a decreased utilization of carbohydrate and an increased utilization of fat, there is no constant parallelism between the degree of lipemia and the degree of glycosuria.

The action of cortical hormone in promoting mobilization of fat from the fat depots is indicated by the experiments of Verzár and Laszt (12), who found that adrenalectomy prevents the development of a fatty liver in animals poisoned with phosphorus, and that the administration of adrenal cortical extract restores the ability of the adrenalectomized animal to develop a fatty liver when poisoned with phosphorus. It is well known that the fat deposited in the liver in phosphorus poisoning is derived from the fat depots. The simplest explanation of the lipemia in the cortisone-treated animals of the present experiment is, of course, that it represents fat mobilized in excess from the fat depots by the action of the excess cortical hormone; but even though this be the case, the manner in which cortisone acts to mobilize the fat from the depots remains obscure, and whether the increased mobilization of fat is a direct effect upon fat metabolism or an effect secondary to other influences exerted by the hormone (*e.g.*, disturbance of carbohydrate metabolism) is not clear at present. It may be remarked that though most of the cortisone-treated animals lost weight, there was no correlation between either the absolute or percentage weight loss and the degree of lipemia (Table I). It remains to be determined whether the increase in total fatty acids is derived mainly from neutral fats or from phospholipides.

The intimate mechanism responsible for this cortisone-induced lipemia requires further investigation, as does also the susceptibility of other animal species, including man, to this effect of cortisone.

SUMMARY

The daily administration of 7.5 mgm. of cortisone to normal adult rabbits kept on a balanced stock diet produces a marked degree of lipemia, with a rise in both the total fatty acids and total cholesterol of the serum, and striking deposits of visible fat in the liver. There is no constant parallelism between the degree of lipemia and the degree of glycosuria.

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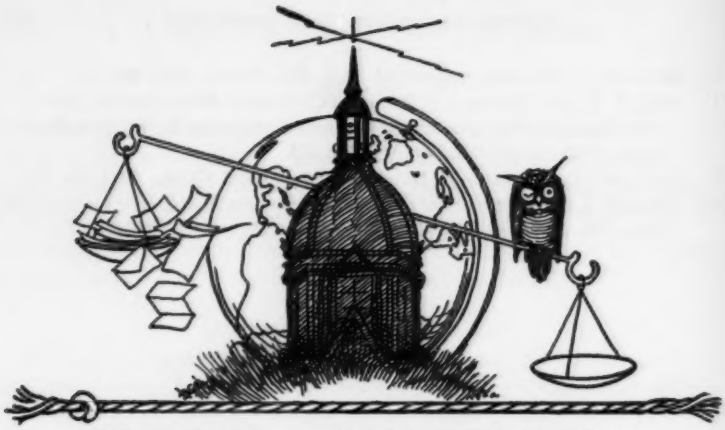

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Essentials of Ophthalmology. By ROLAND I. PRITIKIN. 567 pp. $7.50. *J. B. Lippincott Co., Philadelphia, Pa.*

This book is a newcomer to the ranks of short compendiums of ophthalmology, of which there are already more than a sufficient number. It is therefore pertinent to ask if this volume presents anything novel in the way of presentation and material. Slightly over one-half of this small volume is devoted to short descriptions of the anatomy, embryology and physiology of the eye, to physiological optics, muscle anomalies, refraction, etc. These chapters contain in condensed form the conventional material obtainable in the larger standard text-books. The remainder of the volume is devoted to short descriptions of diseases of the eye and medical ophthalmology, descriptions of surgical procedures being distributed throughout the entire volume, where the author deemed them most appropriate. The result of this condensation is that the latter part of the book is little more than an enlarged dictionary of ophthalmic terms. Many of the various brief statements on the etiology of some disease conditions and on therapeutic procedures will not meet with full agreement among ophthalmologists. The volume contains little of the more recent advances in ophthalmology.

It is somewhat difficult to see just what place this volume will have in ophthalmic literature. Certainly it could not be recommended to undergraduate students and it is entirely too unbalanced and cryptic to be used as a reference book for general practitioners. Perhaps the first half of the book, in which is presented a summary of anatomic details, chemical analysis, etc. could be used by young ophthalmologists cramming for Specialty Board examinations.

W. O.

Surgery of Cataract. By DANIEL B. KIRBY. 695 pp. $30.00 *J. B. Lippincott Co., Philadelphia, Pa.*

No phase of ophthalmic surgery is so simple in principle and yet so intricate in minutiae as cataract extraction. Dr. Kirby has drawn on his vast experience to coordinate the more important of the detailed literature on this subject into a composite volume. It is well organized, completely documented, and contains 339 beautiful illustrations. The rather generous inclusion of direct quotations serves for accuracy of detail but inevitably introduces a degree of repetition and discontinuity which makes for slow reading; this factor, together with the very length of the book, tends to place it in the category of a reference volume.

In Part One, the early history of cataract surgery, consisting principally of couching but occasionally of discission, is recorded in interesting detail. The development of actual cataract extraction (first performed by Daviel in 1748) is traced through the stages leading to present day concepts of such operations. The basic general surgical and scientific principles involved in cataract extraction are reviewed briefly. Sections are devoted to the equipment utilized in the operation, the training and psychology of the cataract surgeon, the preoperative examination of the eye, preoperative criteria for assessing postoperative prognosis, and a classification of the various types of cataract together with the indications and contraindications for operation.

Part Two deals briefly with preparation of the patient for cataract surgery.

Part Three is concerned with the details of present-day surgical technique in discission of the lens, linear extraction, extracapsular cataract extraction, intracapsular cataract extraction, removal of luxated lenses, and removal of traumatic cataracts. It also includes prevention and management of complications during and after operation, postoperative care, and the handling of "after-cataract."

Part Four consists of a discussion of correcting lenses for the aphakic eye and Part Five is concerned with the immediate and final results of cataract surgery.

This volume is particularly valuable not only in that it is relatively complete from the standpoint of a reference book, but also in that the author has exercised a delicate balance of judgement, neither too conservative nor too radical, in his choice of the many alternative procedures and techniques available.

J. S. G.

Pathologic Physiology: Mechanisms of Disease. Edited by WILLIAM A. SODEMAN. 808 pp. $11.50. *W. B. Saunders Co., Philadelphia, Pa.*

To begin with, let it be understood that this book really deserves to be read by every medical student and by every physician engaged in the teaching or practice of internal medicine. Although the title suggests that this is Saunders' answer to Best and Taylor, it is really no such thing; nor is it intended to be. It is a little too advanced and a little too incomplete to be a textbook of physiology. With just a little more it might be a standard textbook in medicine. It is both of these and neither; it is something in between. In short, it is a departure and a welcome one. Since the effort is such a good one, as will be emphasized in a mo-

ment, it is a pity that the publishers appear to have tried to price it out of the market.

Dr. Sodeman has collected a series of authoritative monographs by competent workers elaborating the rational basis for and consequences of altered function, the integral of which we call disease. Space was apportioned sensibly with a single impressive exception: only one page, or about 0.08 per cent of the total book, considers diseases of muscle and the nervous system.

Inventory reveals five chapters (191 pages) on the circulatory system, two chapters (51 pages) on the respiratory system, six chapters (109 pages) on the digestive system, two chapters (125 pages) on the blood and spleen, a chapter each on the urinary tract, on the endocrine glands, on water balance, on nutrition, and on the locomotor system. There are five chapters (73 pages) on infectious diseases and allergy, dedicated primarily to consideration of principles and not to the specific clinical manifestations of any single disease. And finally there are two chapters concerned with physical, toxic and chemical agents.

While this recital reveals the breadth of the book, it is the depth of each offering that makes it remarkable. The monographs, of course, vary in texture. Only one was ill conceived. The rest varied from adequate to masterly, with the skewness quite a bit on the side of excellence. Several of the expositions are classics of lucid compression. Generally the contributors confess to an essential dogmatism more or less demanded by the restrictions of space and the pedagogic impulse to render rational those events that have yet resisted measurement. This approach has been used to the advantage of the reader particularly by E. C. Reifenstein, Jr. who has organized the mass of endocrinology in a clear, orderly, logical and easily remembered way.

A special word must be said for the brilliant contribution of William B. Castle. Eschewing simplification at the expense of accuracy, Dr. Castle has written a memorable conservative and critical essay on disorders of the blood.

Again, in general, the illustrations are well pointed and there is a helpful index. With the exception of Dr. Castle's piece the bibliographic references are inadequate. So many broad and stimulating statements are made throughout the book, an effort should have been made to permit the student to pursue the truth to its source. The editing is of a high order; only one hair-raiser was unearthed: the use of hypothecate for hypothesize.

Finally, if prejudice be pertinent, here is a tome of reasonable displacement and temperate tonnage. Incorporating much medical fundament in modest bulk, it can be read in bed without fear of compression fracture or risk of ruptured viscus.

K. L. Z.

The Pathogenesis and Pathology of Viral Diseases. Edited by JOHN G. KIDD. 235 pp. $5.00. *Columbia University Press, New York.*

With the current rash of books on viruses, one might well question the advisability of publishing a year and a half after it was written, a collection of papers

delivered at a conference at the New York Academy of Science. Yet chick embryo techniques, purification procedures, electron microscopy, neutralization tests and such tend to make one forget that the fundamental problem of virus effect is the reaction of the infected cells. Understanding of how a virus "grows" and how it "kills" must eventually have a morphological as well as a biochemical description. This book is a timely re-emphasis of this. Buddingh's chapter presents just this story, of the effect of the virus on the embryo. Howe brings diverse data to bear on the neuronotropic characteristics of the poliomyelitis virus, and Fenner uses an infection of mice, ectromelia, as a model for studying the spread of a virus through the host. Shope's chapter on the spread of viruses from infected to susceptible hosts, brings to light more scattered data from animal pathology, emphasizing that all is not known about the natural history of virus diseases. Peculiar hosts for virus parasites themselves carry virus from one animal to another. An acute hemolytic disease of dogs "salmon poisoning" seems to be a virus transmitted through a helminthic parasite of the fish.

The editor of this group of talks is to be complimented on gathering together a refreshing group of essays with many fundamental ideas.

F. B. B.

Viruses 1950. Edited by M. DELBRUCK. 147 pp. $2.50. *California Institute of Technology, Pasadena, California.*

The primary purpose of this conference seems to have been to expedite the effect of the studies of bacteriophage and the theories regarding bacteriophage multiplication upon the study of viruses in general. Thus, although the conference was not entirely devoted to the "viruses of bacteria," it does start with Luria's beautifully thought out article on "Bacteriophage. An Essay on Virus Reproduction," and end with a very fine syllabus on methods and techniques used in the study of bacteriophage. It is a unique record, for the animal and plant pathologists present were forced to turn their thoughts to the questions of fundamental nature involved in the dependence of virus upon cell and think in terms of breakdown and reconstruction of individual viral units.

The excellent series of essays on such subjects as "Hemagglutination as Applied to the Study of Virus Infection" by Hirst, or "Masking, Transformation and Interepidemic Survival of Animal Viruses" by R. E. Shope, demonstrate that the technique of study of viruses other than bacteriophage is slower and thus knowledge acquired more slowly. Yet, they show also that any attempt to force the knowledge of animal and plant virology into a framework of bacteriophage knowledge is premature and these authors eschew such attempts.

The idea of publishing this conference was excellent, and this record of discussion will serve for years to come as a stimulus to the search for new facts concerning that interwoven mosaic of dependence which is called the virus-host cell relationship.

F. B. B.

Plastic and Reconstructive Surgery. By FERRIS SMITH. 895 pp. $15.00. *W. B. Saunders Co., Philadelphia, Pa.*

Dr. Smith has written a thoughtful text for the surgeon who is already well grounded in the principles of plastic surgery. It is not intended as a text for the medical student or beginner in the field of reconstruction.

Dr. Smith feels that plastic surgeons since World War I have neglected some of the older principles and tended to emphasize tube pedicles, conveyed flaps, and free grafts. In his large personal experience over a period of thirty-five years, he has come to feel that the careful use of local tissues in the repair of facial defects will often give the optimum correction of the patient's cosmetic disability.

This text is not intended to give all of the useful plastic procedures in use and it is written with as much emphasis on the "don'ts" of reconstruction as on the "do's."

The book is quite well illustrated with 592 prints and diagrams. Throughout the book are numerous careful case reports with details of treatment that are often omitted in more conventional texts.

The body of the text is divided into fourteen sections. These deal with general considerations, clefts and fractures of the face, general surgical measures, operative procedures, then six chapters on anatomical regions about the head, and finally sections on the neck, facial bones, the trunk and extremities.

There is a very nice section on hypospadius written by Drs. Reed N. Nesbit and William Butler. There is no material on reconstruction of the vagina or of the repair of tendon injuries in the hand.

Dr. Smith will always be remembered for his emphasis on gradual partial excisions, and the various uses of local tissue, and this book will probably be the classic treatise on that subject for years to come.

There is an excellent selective bibliography in the book that is nicely arranged according to subject.

M. T. E.

The First Anesthetic—The Story of Crawford W. Long. By FRANK KELLS BOLAND. 160 pp. $3.00. *University of Georgia Press, Athens, Georgia.*

Dr. Boland presents new and documented material to substantiate his firm belief in Long's having administered the first ether anesthesia for surgery. A brief outline of surgery in the pre-anesthetic period and events leading up to the first operation are given. An interesting biographical sketch, including Dr. Long's preparation for surgery gives little doubt of his sincerity and honesty. Crawford Long's life was no exception that "In the realm of observation chance only favors the mind prepared." Had he had a Dr. Henry Hurd to council him he undoubtedly would have reported his cases promptly and often. In so doing little ground would have been left for the Ether Controversy which has continued for more than a century. With considerable new documentary evidence the author has made an interesting and strongly convincing argument in favor of Dr. Long. Adherents to the premise that Crawford W. Long was first to administer ether for surgical anesthesia will be pleased to see his case so ably presented.

O. L. B.

A Textbook of Gynecology, 6th edition. By ARTHUR HALE CURTIS. 799 pp. $10.00. *W. B. Saunders Co., Philadelphia, Pa.*

The desire of the senior author, Arthur Hale Curtis, to share responsibility of preparation with one more intimately in touch with academic activities in gynecology, introduces John William Huffman as co-author of the sixth edition of their textbook of gynecology. The contributions of the junior author are most apparent in the sections on Embryology and Urinary Tract Problems of Gynecology. Much of this work is original with Dr. Huffman, but is presented for the first time in correlated form.

The book remains a text for the student and general practitioner by presenting the essentials of anatomy, physiology, pathology and treatment. While the classic procedures of surgery are described in detail, the newer concepts of therapy such as those of endocrinology are wisely generalized. An excellent review of accepted principles is given, but specific pharmaceuticals and dosages, which would rapidly date the text, are not used.

The section on the female pelvis and perineum is clearly and excellently illustrated. A common terminology between the plates and the text show close association of the senior author and Mr. Tom Jones, the artist.

R. P. O'D.

Reports on Biological Standards: VI. The Design of Toxicity Tests. By W. L. M. PERRY. Medical Research Council, Special Report Series No. 270. 51 pp. 1s 6d. *His Majesty's Stationery Office, London.*

This report deals with the rationale and design of tests of toxicity of pharmacological substances, where the tests depend upon biological response and involve comparison of a test batch with a standard. Two types of response are considered, the all-or-none (quantal) response, such as death or survival, and the graded response such as length of life. The report analyzes several experimental designs, considers the principles behind them, their relative efficiency, and makes recommendations on the basis of this analysis. The problem of the combinaton of results from different experiments is also considered. Arithmetic examples are given to illustrate the procedures.

The literature in the field of bioassay is for the most part concerned with methods of analyzing results of experiments and there is relatively little on the merits of different experimental designs. This is a useful contribution in this field.

M. M.

Freud. Dictionary of Psychoanalysis. Edited by NANDOR FODOR AND FRANK GAYNOR, with a Preface by THEODOR REIK. 208 pp. $3.75. *Philosophical Library, New York.*

The authors wish to permit one to see precisely what Freud said on any given topic by listing terms in alphabetic order and giving one or several quotations under this heading. They hope to help avoid misquotation and misinterpretation of the master. The book makes a handy source of rapid reference and very inter-

esting browsing. Its many shortcomings give it limited value. Freud's determination to fathom the mysteries of human behavior was carried on with a scientific fervor that led to many changes in perspective. He was not a disciple and was not bound to orthodoxy. Quotations bereft of their temporal setting in Freud's development or taken out of the context of the intent of an essay can be extremely misleading. The work is far from comprehensive, and the selections of many quotations rather than others pertinent to the topic, seems quite arbitrary. However, the reviewer detects no particular bias in the selection. To be really useful the book would need to contain many more quotations on many topics and perhaps include editorial comment on the context of the quotations. As long as the volume does not serve as a major source of reference to Freud or a means by which reading the original can be avoided, it can be considered an interesting and useful book to have around.

T. L.

The Merck Manual, 8th Edition. 1592 pp. $5.00. *Merck and Co., Inc. Rahway, N. J.*

The Merck Manual is a good although condensed textbook of general medicine. As a handbook ought to be, it is small (11.5 cm. x 17.4 cm. x 3.7 cm.) and light (0.63 k). The authors are anonymous, consisting of the "Editor," and a board of staff physicians assisted by more than 100 outstanding nameless clinicians. The manual is divided into two parts. The first portion consists of discussions of the diseases afflicting twenty different systems. These chapters vary in their development but in general cover symptomatic management as well as etiology, pathology, diagnosis and treatment of specific disease entities; and this is done in a fashion that conforms neatly to be best current formulations. The material on new drugs is as up-to-date as last Sunday's newspaper and a good deal more conservative. There are few erroneous therapeutic recommendations, and of these the following should be noted: 1) the use of ammonium chloride as a diuretic should be limited to three day periods rather than the recommended 1–2 weeks (p. 125); 2) the dosage of penicillin in the treatment of subacute bacterial endocarditis should be higher and continued longer (p. 178); 3) the dose of diphtheria antitoxin should be larger (p. 706); 4) sodium sulfadiazine should not be given subcutaneously as it is quite alkaline (p. 993).

Part Two contains various useful data on bedside and office procedures, laboratory tests (with normal values), diets and a helpful section on proprietary agents with the aid of which the physician can discover whether "Paxonin" is a pediculocide or an anti-spasmodic.

The deficiencies of this manual arise largely from the abridgment of its material. The practicing physician will find here little to aid him in the problems he meets daily. However, for quick help in unaccustomed problems such as chemical poisoning, this volume is ideal. In addition, it will be found useful by biologists, chemists, lawyers and others who though not clinicians have frequent need for clinical orientation. This manual can be highly recommended for those who need a hasty accurate solution for an unfamiliar clinical situation.

C. G. Z.

BOOKS RECEIVED FOR REVIEW

Conference on Cybernetics. Transactions of the Sixth Conference, March 24–25, 1949. Edited by HEINZ VON FOERSTER. 209 pp. $3.50. *Josiah Macy, Jr. Foundation, New York.*

The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. By LAWSON WILKINS. 384 pp. $13.00. *Charles C. Thomas, Springfield, Illinois.*

The First Anesthetic. By FRANK KELLS BOLAND. 160 pp. $3.00. *University of Georgia Press, Athens, Ga.*

History of the Woman's Medical College. By GULIELMA FELL ALSOP. 256 pp. $4.00. *J. B. Lippincott Co., Philadelphia, Pa.*

The Pathogenesis and Pathology of Viral Diseases. Edited by JOHN G. KIDD. New York Academy of Medicine, Section on Microbiology, Symposium No. 3. 235 pp. $5.00. *Columbia University Press, New York.*

The Physician Examines the Bible. By C. RAIMER SMITH. 394 pp. $4.25. *Philosophical Library, New York.*

Principles and Practice of Surgery. By JACOB K. BERMAN. 1378 pp. $15.00. *The C. V. Mosby Co., St. Louis, Missouri.*

Principles of General Psychopathology. An Interpretation of the Theoretical Foundations of Psychopathological Concepts. By SIEGFRIED FISCHER. 327 pp. $4.75. *Philosophical Library, New York.*

Principles of Internal Medicine. Edited by T. R. HARRISON, M. M. WINTROBE, PAUL B. BEESON, WILLIAM H. RESNIK, AND GEORGE W. THORN. 1590 pp. $12.00. *The Blakiston Co., Philadelphia, Pa.*

Problems of Infancy and Childhood. Transactions of the Third Conference, March 7–8, 1949. Edited by MILTON J. E. SENN. 156 pp. $1.25. *Josiah Macy, Jr. Foundation, New York.*

Progress Volume to accompany Hyman's Integrated Practice of Medicine. Contains cross reference to the original 4 volumes and an index system to all 5 volumes. Prepared by HAROLD THOMAS HYMAN. 734 pp. $10.00. *W. B. Saunders Co., Philadelphia, Pa.*

Renal Function. Transactions of the First Conference, October 20–21, 1949. Edited by STANLEY E. BRADLEY. 172 pp. $2.50. *Josiah Macy, Jr. Foundation, New York.*

Researches in Binocular Vision. By KENNETH N. OGLE. 345 pp. $7.50. *W. B. Saunders Co., Philadelphia Pa.*

Surgery of the Shoulder. By ANTHONY F. DEPALMA. 438 pp. $17.50. *J. B. Lippincott Co., Philadelphia, Pa.*

A Syllabus of Laboratory Examinations in Clinical Diagnosis. Edited by THOMAS HALE HAM. 496 pp. $5.00. *Harvard University Press, Cambridge, Mass.*

A Text-book of X-ray Diagnosis. 2nd edition. By British Authors in Four Volumes. Vol. 2. Edited by S. COCHRANE SHANKS AND PETER KERLEY. 830 pp. $18.00. *W. B. Saunders Co., Philadelphia, Pa.*

Viruses 1950. Proceedings of a Conference on the Similarities and Dissimilarities between Viruses Attacking Animals, Plants, and Bacteria, Respectively. Held at the California Institute of Technology, March 20–22, 1950. Edited by M. DELBRUCK. 147 pp. $2.50. *The Division of Biology, California Institute of Technology, Pasadena, California.*